Appeal No. 13-1406

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

TAKEDA PHARMACEUTICAL COMPANY LIMITED,
TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,
TAKEDA PHARMACEUTICALS, LLC,
TAKEDA PHARMACEUTICALS AMERICA, INC., and ETHYPHARM, S.A.,

Plaintiffs-Appellees,

v.

ZYDUS PHARMACEUTICALS USA, INC.
and CADILA HEALTHCARE LIMITED,

Defendants-Appellants.

On Appeal from the United States District Court
for the District of New Jersey in Case No. 10-CV-1723,
Honorable Joel A. Pisano

NON-CONFIDENTIAL OPENING BRIEF FOR DEFENDANTS-APPELLANTS

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CONFIDENTIAL MATERIAL REDACTED

Defendants' Opening Brief contains detailed discussions of sensitive, proprietary, highly-confidential information concerning Zydus's ANDA product at issue, Zydus's communications with the United States Food and Drug Administration which are not publicly available, and the basis for certain of the proprietary business decisions made by Defendants. None of this information has been shared with any non-parties to this litigation or otherwise made publicly available. Moreover, portions of the testimony of parties' respective witnesses related to infringment were sealed by the district court as were portions of the district court's opinion. Pursuant to Federal Circuit Rule 28, all references to sealed information and documents, including the substance thereof, have been redacted in the Nonconfidential version of Defendants' Opening Brief, and enclosed in brackets in the Confidential version of Defendants' Opening Brief, filed concurrently via ECF.

Defendants-Appellants Zydus Pharmaceuticals USA, Inc. ("Zydus") and Cadila Healthcare Limited ("Cadila") (collectively, "Defendants") appeal from the May 7, 2013 final judgment entered against Defendants (D.I. 346, Joint Appendix ("J.A."), at JA0058), including the district court's claim construction rulings (JA0106), as well as the May 7, 2013 Permanent Injunction entered against Zydus in connection with the entry of final judgment. D.I. 346, JA0058.

I
STATEMENT OF RELATED CASES

Pursuant to Rules 28 and 47.5 of the Rules of this Court, Defendants' undersigned counsel states:

1) On November 26, 2012 Defendants filed a notice of appeal with this Court appealing a district court order extending the statutory 30 month stay of the approval of Zydus's abbreviated new drug application ("ANDA") at issue in this case. *See*, *Takeda Pharm. Co., Ltd., et al. v. Zydus Pharm.'s USA, Inc., et al.*, docket no. 13-1089. That appeal, which did not address any of the matters at issue in this appeal, was resolved by agreement and voluntarily withdrawn. *Id.*, at D.I. 65.

2) Counsel is not aware of any other case pending in this or any other court that will directly affect, or be directly affected by, this Court's decision in the pending appeal.

II
JURISDICTIONAL STATEMENT

This case involves allegations of patent infringement stemming from Zydus's filing of an ANDA with the United States Food and Drug Administration ("FDA") to obtain approval to market and sell a bioequivalent version of Plaintiffs-Appellees ("Plaintiffs"),[1] Prevacid® SoluTab™ (ODT) product ("Prevacid"). This appeal arises from the district court's final judgment in Plaintiffs' favor on: 1) Plaintiffs' claim that Zydus's proposed ANDA product infringes claim 1 of United States Patent No. 6,328,994 (the "'994 Patent"); and 2) Defendants' counterclaims for declaratory judgment of noninfringement and invalidity. S*ee*, D.I. 346, JA0104. Zydus, but not Cadila, was also permanently enjoined from "engaging in the commercial manufacture, use, offer for sale or sale within the United States, or importation into the United States, of Zydus's proposed ANDA product until the expiration of the '994 Patent." *See*, *Id.* This Court has jurisdiction over this appeal pursuant to 28 U.S.C. §1295(a)(1).

[1] Ethypharm, S.A. sought relief only with respect to United States Patent No. 5,464,632 (the "'632 Patent"). All claims related to the '632 Patent were resolved prior to trial and the '632 Patent has expired. *See*, May 7, 2013 Sealed Opinion [D.I. 345] ("Opinion"), at 3, JA0058.

III
STATEMENT OF THE ISSUES

1. Whether the district court properly construed the claim term "average particle diameter of 400 μm or less" in claim 1 of the '994 Patent to mean "fine granules up to and including the enteric coating layer having an average particle diameter of 400 μm (± 10%) or less" when the intrinsic evidence unquestionably leads to a different construction and the extrinsic evidence relied upon by the district court postdates the '994 Patent application by five or more years?

2. Whether the district court's finding that Zydus's proposed ANDA product infringes claim 1 of the '994 Patent is clearly erroneous given that the finding of infringement is premised upon multiple findings of fact not supported by the record evidence?

3. Whether Defendants proved by clear and convincing evidence that claim 1 of the '994 Patent, the only asserted claim, is invalid for: i) failure to satisfy the written description requirement of 35 U.S.C. § 112; ii) lack of enablement under 35 U.S.C. § 112; and iii) indefiniteness?

IV
STATEMENT OF THE CASE

A. Preliminary Statement

In February 2010 Zydus filed an ANDA with the FDA seeking approval to market and sell a bioequivalent version of Prevacid. Opinion, at 3, JA0060. Plaintiffs commenced the underlying action in April 2010, alleging that Zydus's

proposed ANDA product infringed multiple claims of several patents. *Id.* By the time trial commenced on March 26, 2013, only claim 1 of the '994 Patent remained at issue. *Id.*, at 4, JA0061.

Claim 1 of the '994 Patent claims an orally disintegrable tablet containing enteric coated lansoprazole granules with an average particle diameter of 400 μm or less. DTX 2, at claim 1, JA5630.[2] The enteric coated granules are intended to form a suspension in the mouth that is easy to swallow upon tablet dissolution. Fennerty Dir., 53(8-12); 53(19)-54(9); 63(14-18), JA3691-92; JA3701.[3] The enteric coated granules of claim 1 are "fine" granules with an average particle diameter of about 400 μm or less. DTX 2, at claim 1, JA5630; col. 5, lns. 57-64, JA5614. In the specification of the '994 Patent the "fine" granules of the invention are explicitly distinguished from "conventional" granules, those with an average particle diameter of 400 μm or more which are indicated to cause an undesired

[2] "DTX" refers to Defendants' Trial Exhibit; "PTX" refers to Plaintiffs' Trial Exhibit.

[3] Trial testimony of the parties' respective witnesses referenced herein is cited as follows: "Brittain Dir." or "Brittain Cross" refers to the testimony of Defendants' expert Dr. Harry Brittain; "Meyer-Stout Dir." or "Meyer-Stout Cross" refers to the testimony of Defendants' expert Dr. Paula Meyer-Stout; "Bugay Dir." or "Bugay Cross" refers to the testimony of Plaintiffs' expert Dr. David Bugay; "Byrn Dir." or "Byrn Cross" refers to the testimony of Plaintiffs' expert Dr. Stephen Byrn; and "Fennerty Dir." or "Fennerty Cross" refers to the testimony of Plaintiffs' witness Dr. Brian Fennerty.

feeling of roughness in the mouth upon tablet dissolution and release of the enteric coated granules, and lead to "inferior workability" when dispensing. Brittain Dir., 255(22)-256(19), JA3893-94; DTX 2, at col. 2, lns. 12-22, JA5612. The evidence showed that Zydus designed around claim 1 of the '994 Patent by manufacturing a bioequivalent product using "conventional" granules.

The district court conducted *Markman* proceedings and on October 5, 2011 issued claim construction rulings. The district court adopted Plaintiffs' construction for the claim term "fine granules having an average particle diameter of 400 μm or less" in claim 1 of the '994 Patent and construed it to mean "fine granules up to and including the enteric coating layer having an average particle diameter of 400 μm (± 10%) or less." October 5, 2011 *Markman* Opinion, [D.I. 113] ("*Markman* Opinion"), at 7, JA0112. In construing that claim term the district court ignored the explicit definitions of "fine" granules and "conventional" granules in the '994 Patent's specification. Instead, the district court relied upon extrinsic expert testimony and references that post-date the 1999 filing of the application leading to issuance of the '994 Patent by five or more years. *See*, United States Pharmacopeia ("USP") <429>, Light Diffraction Measurement of Particle Size, first published in 2004, and PQRI Recommendations on Particle-Size Analysis of Drug Substances Used in Oral Dosage Forms, published in June 2007, exhibits 5 and 6 to the December 3, 2010 Declaration of Dr. Stephen R. Byrn in

Support of Plaintiffs' Opening Claim Construction Brief ("Dec. 3 Byrn Decl."), JA0294-321. The district court also ignored at trial statements made in a continuation application of the '994 Patent that made clear that Plaintiffs were estopped from asserting that "average particle diameter of 400 μm or less" meant anything over 400 μm. *See*, DTX 9, at JA7228 ("By having the average particle diameter of the granules within 400 μm, the feeling of roughness in the mouth can be prevented.")

The district court's claim construction opinion focused on the word "about" preceding 400 μm in the definition section of the specification, *see* DTX 2, at col. 5, lns. 57-64, JA5614, irrespective of the fact that the exact phrase equated to "about 400 μm" is not found in claim 1 of the '994 Patent. *Markman* Opinion, at 6, JA0111, DTX 2, at claim 1, JA5630. The district court ignored the evidence in the specification that the term "about" is intended to be a downward directive as references to an average particle diameter of "about" 400 μm are consistently followed by average particle diameter measurements of less than 400 μm:

> The average particle a (sic) diameter of the included granules must be about 400 μm or less, preferably about 350 μm. DTX 2, col. 2, lns. 20-22 (emphasis added), JA5612.
>
> * * *
>
> The "fine granules" have an average particle diameter of about 400 μm or less, preferably 350 μm or less. Preferably the average particle diameter of the fine granules is 300 to 400 μm. DTX 2, col. 12, lns. 58-61, (emphasis added) JA5617.

See, also, DTX 2, at col. 5, lns. 57-64, JA5614. By using the word "must" in their description of the average particle diameter of the included granules, and in teaching that granules with even smaller average particle sizes were preferred, as well as explicitly defining "conventional" granules as having average particle diameters above 400 μm, DTX 2, col. 2, lns. 18-20, JA5612, the inventors established "400 μm" as the upper most limit for the average particle diameter of the "fine" granules of the '994 Patent.

Following denial of Defendants' motion for reconsideration of the district court's claim construction ruling, D.I. 130, [redacted]

[redacted]

Zydus specifies a static sampling technique to obtain a representative sample of granules upon which to conduct measurements. Brittain Dir., 335(10-16), JA3973. The district court found such sampling technique inadequate to assure non-infringement, finding only dynamic sampling to be appropriate even though, due to constraints placed on drug manufacturers by the FDA, static sampling was required. *Id*., at 335(17)-336(13), JA3973-74. The district court ignored the fact that nowhere in the specification is there reference to the inventors having limited sampling to dynamic sampling.

The district court rejected Defendants' argument, made both *in limine* and after trial, that [redacted] pursuant to this Court's decision in *Bayer AG v. Elan Pharma. Research Corp.*, 212 F.3d 1241 (Fed. Cir. 2000) ("*Elan*"). *See*, March 20, 2013 Motion *In Limine* Opinion [D.I. 317], at 4, JA2549; Opinion, at 22-24, JA0079-81. The district court rejected Zydus's argument based on *Elan* following trial primarily because the district court found that Zydus failed to deagglomerate, or artificially separate by software means, granules having two

or more cores prior to conducting average particle diameter measurements. Opinion, at 23, JA0080. The district court reached this conclusion even though no evidence was presented that the patentee had ever deagglomerated, artificially or otherwise, hard agglomerates in respect of the recited average particle diameter in the specification or with respect to the average particle diameter measurements reported to the USPTO in overcoming prior art in the prosecution file history. *See*, DTX 2, at Examples 3-9, JA5623-30; DTX 7, JA6139-44.

The process described in the '994 Patent for the manufacture of enteric coated granules starts with individual lansoprazole cores. *See, e.g.,* DDX 2, at Example 3, JA5623. The cores are then enteric coated via the use of a fluid-bed coating process. *See*, *Id.* *See also*, Brittain Dir., 265(20)-267(20), JA3903-05; Bugay Cross, 214(2-12), JA3852. Both parties' experts agreed that this process inevitably results in a portion of the individual cores becoming cemented together thereby forming single granules with multiple cores. Brittain Dir., 266(12)-267(11), JA3904-05, Bugay Cross, 214(2-12), JA3852. These cemented multi-core granules are referred to as hard-agglomerates. Brittain Dir., 259(1)-260(5), JA3897-98. The '994 Patent does not limit "fine" or "conventional" to granules with single cores, a fact that makes eminent sense as the formation of hard agglomerates during the fluid-bed coating process is inevitable. Brittain Dir., 266(12)-267(11), JA3904-05; Bugay Cross, 214(2-12), JA3852.

The '994 Patent specifically enumerates laser diffraction as the "best mode" for determining average particle diameter, DTX 2, at col. 18, lns. 57-58-col. 19, lns. 35-37, JA5620-21, and in fact such method was utilized throughout the specification and in distinguishing over prior art in the file history. DTX 2, Examples 3-9, JA5623-30; DTX 7, at JA6139-44. It was undisputed that laser diffraction cannot distinguish between hard agglomerate granules and single core granules. Brittain Dir. 313(1-5), JA3951; Bugay Dir., 104(22)-105(4), JA3742-43. The '994 Patent and its file history do not indicate that a measurement methodology other than laser diffraction should be used if hard agglomerate granules are present in the granule sample to be measured, and in fact teaches against the same in the specification examples, in that all measurements were made on all obtained fluid-bed coated granules using laser diffraction analysis. *See*, DTX 2, at Examples 3-9, JA5623-30; DTX 7, at 6139-44. Thus, the inventors themselves measured hard agglomerate granules and included them in average particle diameter determinations.

Plaintiffs argued that laser diffraction was an inappropriate measurement methodology because it could not differentiate between single core granules and hard agglomerates, which by definition have multiple cores. Opinion, at 19, JA0076. Without any support in the specification or file history Plaintiffs argued that laser diffraction is only appropriate when the sample to be measured contains

"nominal" hard agglomerates. *Id.*, at 20, JA0077. Plaintiffs introduced no evidence of what constitutes a "nominal" amount of hard agglomerates, nor did Plaintiffs introduce any evidence of the amount of hard agglomerates found in the obtained granular ensembles of the specification examples or in the examples produced during patent prosecution to overcome prior art. An objected-to statement by Plaintiff's counsel during opening statements that Plaintiffs' commercial product contains a "nominal" amount of hard agglomerates is not evidence and, in any case, is completely irrelevant.

At trial Plaintiffs presented evidence of the average particle diameter of the granular distribution of granules extracted from Zydus's exhibit batch tablets measured via optical microscopy. Hard agglomerates in the distribution were artificially dissected by an operator who placed a virtual line between what he believed was the fusion line of two or more previously separate granules and then "deagglomerated" by software means. Brittain Dir., 293(24)-295(5), JA3931-33. The virtual lines were drawn where the operator subjectively believed the hard agglomerate should be divided into smaller granules. *Id*. It was only because Plaintiffs engaged in this virtual dissection of hard agglomerates that Plaintiffs were able to bring Zydus's proposed ANDA product within the scope of claim 1 as construed; the evidence showed that when hard agglomerates were measured without virtual dissection Zydus's proposed ANDA product was outside the scope

of the claim as construed. DTX 73, JA8338; Brittan Dir., 304(14)-308(25), JA3942-46. Even with this artificial dissection, Plaintiffs faced a conundrum of their own making, *i.e*. that the median particle diameter of the granular distribution, determined by Plaintiffs to be approximately 420 μm, Bugay Dir., 92(18-22), 117(6-11), JA3730, JA3755, constituted "conventional" granules pursuant to an explicit definition in the specification, not "fine" granules as required by claim 1. DTX 2, col. 2 lines 12-22, JA5612. To overcome this conundrum, Plaintiffs asserted the district court could re-write such explicit definition to include a ± 10% variation, while ignoring once more the minus part of such variation even though in this case the "conventional" granules ensembles were defined as more than 400 μm (as compared to claim 1 which recites 400 μm or less and which with respect thereto Plaintiffs assert one applies only the minus part of the variance). DTX 2, col. 2 lines 12-22, JA5612; Bugay Cross., 226(22)-227(3-12), JA3864-65.

Irrespective of infringement the asserted claim is clearly invalid for a multitude of reasons.

First the asserted claim is invalid as not enabled. Plaintiffs vigorously asserted that while the '994 Patent enumerates laser diffraction as a methodology available to the person of ordinary skill in the art ("POSITA") to conduct average particle diameter measurements, it did not limit the techniques that could be used

to determine average particle diameter. *See*, Bugay Dir., 98(15-18), JA3736. Both parties' experts agreed that there are many measurement techniques available for determining average particle diameter each of which measures a different aspect of the granule and thereby provides a different result. Meyer-Stout Dir., 445(1)-448(4), JA4083-86; Byrn Dir., 510(25)-511(16), JA4148-49. Thus, the same granule sample could be both within the scope of the claim and outside the scope of the claim depending on the measurement technique used, and the POSITA would not know whether the product infringed. Meyer Stout Dir., 447(10)-448(4), JA4085-86. Under this Court's reasoning in *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003) asserted claim 1 is clearly not enabled.

Second, claim 1 lacks written description support. The '994 Patent teaches the measurement of fine granules pre-tablet compression, but claims a finished tablet comprising "fine" granules with a specified average particle diameter. Meyer-Stout Dir., 453(10-22), JA4091; DTX 2, at claim 1, JA5630. Dr. Byrn, Plaintiffs' expert, admitted that a granule sample could be non-infringing pre-tableting while infringing post-tableting, Byrn Cross, 550(25)-551(6), JA4188-89; 552(10-17), JA4190, particularly given the wide ranges of tablet hardness permitted by claim 1 ("about 1 to about 20kg" in hardness strengths). DTX 2, at claim 1, JA5630. The '994 Patent does not teach how to measure granules to

ensure that the average particle diameter measurement post-tableting is equivalent to that which would be found pre-tableting. Meyer-Stout Dir., 453(18)-455(13), JA4091-93. Because the '994 Patent teaches the measurement of granules pre-tableting and claims "fine" granules of a certain specified average particle diameter in a finished tablet, but does not teach how to measure granules to ensure the average particle diameter does not change upon tableting, the '994 Patent lacks written description, as in the case of *Eli Lilly v. Teva Pharms. USA, Inc*., 619 F.3d 1329 (Fed. Cir. 2010).

As a result of the district court's construction of 400 μm or less to mean "400 μm ± 10% or less", *see* Opinion, at 42, JA0099, the defined term "fine" granules could now include granules with an average particle diameter of 440 μm, the very defined "conventional" granular ensembles of the specification which are said to cause an undesirable feeling of roughness in the mouth. DTX 2, at col. 2, lns. 12-18, JA5612. The claim construction also creates a range of potential ceilings for claim 1 such that the average particle diameter of the "fine" granules could be anywhere between 360 μm or less, or 440 μm or less, making the claim indefinite. Brittain Dir., 327(9)-328(23), JA3965-66. Lastly, the claim construction invalidates the asserted claim as it allows for the incorporation of numerous inoperative species.

B. Procedural Posture

On May 7, 2013, final judgment entered in Plaintiffs' favor on their infringement claim against Zydus and on Defendants' counterclaims for declaratory judgment of non-infringement and invalidity, enjoining Zydus. D.I. 346, JA0104.

V
STATEMENT OF FACTS

A. The '994 Patent

The '994 Patent is directed to lansoprazole orally disintegrable tablets containing "fine" granules with an average particle diameter of a sufficiently small size so as not to impart a feeling of roughness in the mouth upon disintegration of the tablet and release of the granules. DTX 2, Abstract, JA5611. The infringement dispute centered on whether the enteric coated granules in Zydus's proposed ANDA product fall within the scope of the '994 Patent's definition of "fine" granules, which do not impart a feeling of roughness in the mouth and are within the scope of the claim, or "conventional" granules, which will cause roughness in the mouth and are outside the scope of the claim. DTX 2, at col. 2, lns 12-22, JA5612; col. 5, lns. 51-64; JA5614; claim 1, JA5630.

B. Fine Granules, Conventional Granules, and Maximum Particle Diameter

The '994 Patent defines "fine" granules in terms of the average particle diameter of an ensemble of granules:

> In the present invention, "fine granules having an average particle diameter of 400 μm or less, . . ." have an average particle diameter of about 400 μm or less, in order that roughness is not felt in the mouth. Preferably, the average particle diameter of the fine granules is 300 to 400 μm.

DTX 2, at col. 5, lns. 57-64, JA5614; Brittain Dir., 280(15)-282(2), JA3918-20. The specification limits the maximum particle diameter of the individual granules which can be in the ensemble of "fine" granules to practically 425 μm:

> Aside from the average particle diameter of the above "fine granules", regarding the maximum particle size, the particle diameter is practically 425 μm or less, and preferably practically 400 μm or less. Preferably, the particle diameter is practically 300 to 425 μm, more preferably 300 to 400 μm.

With "practically" meaning the particles may include about 5 weight % or less of inevitable contaminant particles outside the described range. DTX 2, col. 5, ln. 65 – col. 6, ln. 9, JA5614.

The specification distinguishes "fine" granules from "conventional" granules, which cause the undesired feeling of roughness in the mouth:

> Conventional granules have large particle diameters, which results in inferior workability when dispensing . . . . Granules having a large particle diameter (400 μm or more of average particle diameter) also produce a feeling of roughness in the mouth. Accordingly, especially when used in an orally disintegrable tablet, the average particle a [sic] diameter of the included granules must be about 400 μm or less, preferably about 350 μm.

DTX 2, at col. 2, lns. 12-22, JA5612 (emphasis added); *see also*, Brittain Dir., 286(22)-288(5), JA3924-26. The '994 Patent creates a bright line between "fine" granules that do not cause roughness in the mouth and "conventional" granules that do cause roughness in the mouth. *See*, Defendants Demonstrative Exhibit ("DDX") 9, JA3638. That fine line is at 400 μm. Brittain Dir., 288(6)-289(6), JA3926-27. As Dr. Brittain testified: "[t]he patent consistently defines that if you have an ensemble of granules and they [sic] the median particle size is smaller than 400 microns, they are the granules of the invention because they do not cause roughness in the mouth." *Id*.

While the district court agreed that "a stated objective of the invention of the '994 patent is good mouth feel, that is, an ODT containing fine granules that do not cause roughness in the mouth", it found that "good mouth feel/absence of roughness in the mouth is not a limitation in claim 1 of the '994 patent." Opinion, at 6, JA0063. The district court's finding ignores the fact that claim 1 is directed to "fine" granules which are specifically defined as granules of a specific average particle diameter, 400 μm or less, that do not impart a feeling of roughness in the mouth. DTX 2, at col. 5, lns. 57-64, JA5614. Both parties agree that the creation of an ODT containing "fine" granules, those that do not impart a feeling of roughness in the mouth upon tablet disintegration, is the invention. Transcript of

May 26, 2011 Markman Hearing ("*Markman* Tran."), Plaintiffs statement at 12(10-15), JA1266; Brittain Dir., 255(22)-256(19), JA3893-94.

Based on the Plaintiffs' reported average particle diameter of the granular ensemble in Zydus's exhibit batch tablets (those tablets manufactured as part of the ANDA process) as determined via optical microscopy, Dr. Brittain opined that the enteric-coated granules in Zydus' exhibit batch tablets would cause roughness in the mouth. Brittain Dir., 323(11-22), JA3961. Thus, Zydus's exhibit batch tablets contain non-infringing "conventional" granular distributions.

C. The Inventors Utilized Laser Diffraction to Measure Average Particle Diameter

In order to determine whether a particular granular ensemble are "fine" granules or non-infringing "conventional" granules, the POSITA must measure the particle diameter of the granules in the ensemble to determine average particle diameter. The '994 Patent defines "Average Particle Diameter" as "volume based distribution median diameter (median diameter: 50% particle diameter from cumulative distribution), unless otherwise specified." DTX 2, at col. 5, lns. 43-46, JA5614. Adhering to the definition, the parties agreed, and the district court found, that "[m]edian diameter refers to the value where 50 percent of the particles are above that micron size and 50 percent of the particles are below that micron size." Opinion, at 13, JA0070.

Both parties' experts agreed that there are multiple measurement methodologies available to conduct particle size measurements of the granule size discussed in the '994 Patent. *See*, Meyer-Stout Dir., 434(3-11), JA4072; Byrn Dir., 510(25)-511(16), JA4148-49. Several factors dictate that laser diffraction be used in regard to enteric coated granules produced by fluid-bed coating. First, the '994 Patent inventors specifically enumerate laser diffraction as a method to be utilized for determining average particle diameter. DTX 2, col. 5, lns. 46-50, JA5614. In addition, laser diffraction is enumerated in the section of the specification titled: "BEST MODE FOR CARRYING OUT THE INVENTION." DTX 2, col. 18, lns. 56-58; col. 19, lns. 35-37, JA5620-21. Lastly there is nothing in the specification or the claims evidencing that the inventors utilized anything other than laser diffraction to determine average particle diameter even though all of their examples measured average particle diameter of all enteric coated granules obtained immediately after fluid-bed coating, the very process Plaintiffs now assert requires the use of modified optical microscopy. *See* Meyer Stout Dir., 443(8-16), JA4081; DTX 2, at Examples 3-9, JA5623-30.

Second, in distinguishing prior art granules coated using a fluid-bed coating process against granules of Example 9 of the specification, also coated by fluid-bed coating process, Plaintiffs used laser diffraction analysis which again does not

permit virtual deagglomeration. *See*, DTX 7, at JA6139-44; Brittain Dir., 302(15)-303(4), JA3940-41.

Third, the patentee's stated definition of "average particle diameter" directs one of ordinary skill in the art to laser diffraction instrumentation because laser diffraction yields "particle size information directly in the form of a volume based distribution." *See*, Brittain Dir., 269(21)-271(25), JA3907-09.

VI
THE CLAIM CONSTRUCTION PROCEEDINGS

A claim construction hearing was held on May 26, 2011. Among other things, the proper construction of the claim term "average particle diameter of 400 μm or less" in claim 1 of the '994 Patent was argued. *See*, Opinion, at 10, JA0067.

Plaintiffs argued that the claim term should be construed to include a deviation of ± 10% based on particle size measurements conducted using laser diffraction technology, the sole measurement technique utilized by the inventors. *Markman* Tran., at 17(20)-18(21), JA1271-72. Plaintiffs' specifically argued that the '994 Patent directs the POSITA to laser diffraction instrumentation for conducting average particle diameter measurements and that the ± 10% deviation would be recognized by a POSITA to be the deviation associated with laser diffraction analysis. *Id*. In support of their proposed claim construction Plaintiffs primarily relied upon testimony of their claim construction expert, Dr. Byrn, and two extrinsic references, both of which relate to laser diffraction technology and

both of which were published at least five years after the filing of the application leading to the issuance of the '994 Patent. *See* Dec. 3 Byrn Decl., Exs. 5 and 6, JA0294-321.

While Defendants agreed that the POSITA would be directed to laser diffraction analysis, Defendants argued, however that the claim term should be construed as "fine granules having an average particle diameter of precisely 400 μm or less . . .". to account for instrument precision and error. *See*, *Markman* Opinion, at 4, JA0109. During the hearing Defendants strongly urged the Court that the ± 10% deviation advocated for by Plaintiffs would invalidate the claims as it would make the claims insolubly ambiguous by making the upper limit undeterminable. *Markman* Tran., at 45(11-21), JA1299. The district court relied upon Plaintiffs' extrinsic evidence and adopted Plaintiffs' proposed construction of "fine granules up to and including the enteric coating layer having an average particle diameter of 400 μm (± 10%) or less." *Markman* Opinion, at 7, JA0112. This construction substantially expanded the scope of claim 1 to reach "conventional" granules which cause a feeling of roughness in the mouth.

VII
DESPITE THEIR ADVOCACY OF LASER DIFFRACTION TO OBTAIN THEIR DESIRED CLAIM CONSTRUCTION, PLAINTIFFS UTILIZED A DIFFERENT MEASUREMENT TECHNIQUE TO "PROVE" INFRINGEMENT

A. Hard Agglomerates Are Granules Consisting of Two or More Lansoprazole Cores That Inevitably Form During the Fluid-Bed Coating Process Used by The Inventors and Defendants To Manufacture Product

The infringement determination turned on whether the measurement of average particle diameter of a given granular ensemble is limited to granules with single cores such that hard agglomerates, *i.e.*, granules that become cemented together during the manufacturing process and as a result include two or more lansoprazole cores, should be artificially separated by software into single cores, Brittain Dir., 265(20)-267(20), JA3903-05, a process that is not possible using laser diffraction. Meyer-Stout Dir. 444(13-19), JA4082. There is confusion in the relevant art concerning the use of the term "agglomerate" and that term is often used to mean different things. *See*, Bugay Cross, 158(5-12), JA3796; Brittain Dir., 259(2)-260(5), JA3897-98. Defendants remedied this confusion at trial by distinguishing "hard agglomerates," granules that are "irrevocably fused together in such a way that they can only be considered as an individual particle," from "soft agglomerates," granules that are clumped together but not "fused or cemented together." Brittain Dir., 259(20)-260(5), JA3897-98.

Hard agglomerates are formed during the fluid-bed coating process utilized by Defendants, Plaintiffs, and the inventors of the '994 Patent in the manufacture of enteric coated granules. Brittain Dir., 265(20)-267(11), JA3903-05; DTX 2 at Examples 3-9, JA5623-30. The formation of hard agglomerates is inevitable when that process is utilized. Brittain Dir., 265(20)-267(24), JA3903-05; Bugay Cross, 214(6-12), JA3852. During the fluid-bed coating process some fraction of the granules collide with one another and stick together. Brittain Dir., 265(20)-267(11), JA3903-05. The coating cements the granules together, forming a hard agglomerate. *Id*. Although the granule may have two or more cores, it is a single granule for average particle diameter determination. Brittain Dir., 266(12)-267(11), JA3904-05. Plaintiffs' recognized this very fact early on in this case when they represented in their Local Rules Infringement Contentions that: "Zydus' ANDA states that its Proposed Drug Product contains enteric-coated pellets. The enteric-coated pellets are fine granules." DTX 30, at pg. 3, JA8158. The fact that Zydus's ANDA includes an idealized granule with a single-core does not eliminate the fact that the formation of hard agglomerates is inevitable and that hard agglomerates are to be included in the determination of average particle diameter of the fine granule ensembles.

Despite the inevitable formation of hard agglomerates during the fluid-bed coating process, Plaintiffs argued, and the district court found, that the '994 Patent

requires average particle diameter measurements to be made on granules with single cores so that hard agglomerates should be virtually dissected according to the number of cores. Opinion, at 12, JA0069 ("Nowhere does the '994 Patent teach that a "fine granule" can be built from more than one spherical core."). Hard agglomerates are not built, they are inevitably formed during the coating process. Plaintiffs offered no evidence to the contrary.

B. All Reported D_{50} Measurements to the USPTO and As Specified by the Claims Report Hard Agglomerates As Individual Granules

Measurements of granules made by the inventors, as well as Zydus, are not made on the underlying granule cores. Instead, measurements are conducted after the fluid-bed coating process and formation of hard agglomerates. Brittain Dir., 265(20)-267(11), JA3903-05. Examples 3-9 in the '994 Patent describe a process wherein granules are sieved after the fluid-bed coating process. DTX 2, at Examples 3-9, JA5623-30. The post-fluid-bed coating process "obtained granules" are then immediately measured using laser diffraction instrumentation for purposes of determining average particle diameter. *Id*. While sieving reduces the amount of hard agglomerates, some invariably pass the mesh openings due to the shaking of the sieve and the shortest diameter of the hard agglomerate. Likewise, when comparing the average particle diameter of the granular distribution of Examples of EP761212 versus Example 9 of the Patent specification in a declaration submitted to the USPTO by named inventor Toshihiro Shimizu (Paper No. 9), the

particle diameter of all the obtained granules were utilized in determining average particle diameter including hard agglomerate granules. *See*, DTX 7 at, JA6139-44.

C. Plaintiffs' Infringement Evidence is Derived From Measurements Made Using Optical Microscopy On Virtually Dissected Granules

Zydus manufactured exhibit batch tablets in connection with its ANDA filing in 2009 and manufactured a second batch in connection with a response to a FDA inquiry in 2012. Brittain Dir., 277(22)-278(13), JA3915-16. There was no difference in the manufacturing process of the 2009 exhibit batch tablets and 2012 exhibit batch tablets. *Id*. Plaintiffs' expert performed testing on granules extracted from tablets from both exhibit batches and agreed that both are relevant to the infringement analysis. Bugay Cross, 150(1-11), JA3788.

Plaintiffs' expert used optical microscopy to determine the average particle diameter of granules extracted from Zydus's exhibit batch tablets. Opinion, at 20, JA0077. Although they used optical microscopy, Plaintiffs presented no proof that the variance associated with this technique was the same as associated with laser diffraction employed in sampling large bulks (not measuring all the granules in a tablet), the technique upon which the ± 10% of variation in the claim construction was founded.

Plaintiffs argued that the use of laser diffraction to determine average particle diameter is only appropriate when there are a "nominal" amount of hard

agglomerates present in the sample. *Id*. Plaintiffs introduced no evidence as to what is meant by a "nominal" amount of hard agglomerates. Plaintiffs also introduced no evidence as to the amount of hard agglomerates in Plaintiffs' exemplar granules (set forth in the specification). Nor did Plaintiffs point to anything in the '994 Patent specification or claims directing the POSITA to a different measurement technique if the amount of hard agglomerates exceeds a certain specified amount or percentage. All the '994 Patent teaches is measurement by laser diffraction of the actual granules obtained after the fluid-bed coating and sieving process. *See*, DTX 2, at Examples 3-9, JA5623-30. This is the exact process followed by Zydus.

Plaintiffs' expert utilized Cilas ExpertShape Software with an optical microscope to measure average particle diameter of the granules extracted from Zydus's exhibit batch tablets. Opinion, at 20, JA0077. Following extraction the granules were placed on slides. Brittain Dir., 291(2)-292(15); JA3929-30. Plaintiffs' expert then used a virtual line module to dissect the hard agglomerates- an aspect of the software which is only to be used to delineate granules that are simply touching by placing virtual lines on pixilated images viewed under the microscope. *See*, DTX 35, JA8171-238; Brittain Dir., 310(11)-312(4), JA3948-50. The virtual line instructs the software that these granules are separate and to treat them as individual granules in determining average particle diameter. *See*, Brittain

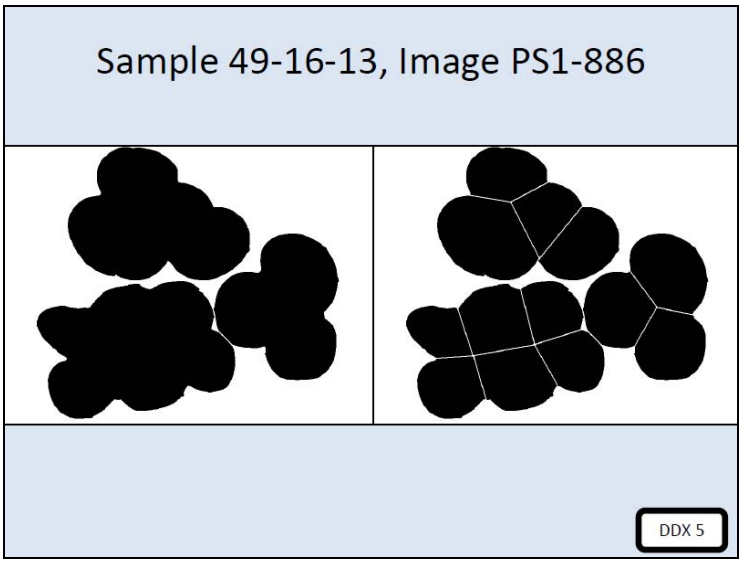
Dir., 292(21)-293(18), JA3930-31; 310(11)-312(4), JA3948-50. Separating granules that are simply touching by drawing a line prior to conducting measurements is an appropriate and acceptable use of the Cilas ExpertShape software, but using the virtual line module to divide hard agglomerates is not. Brittain Dir., 292(21)-293(18), JA3930-31; 311(13)-312(24), JA3949-50. *See also*, DTX 35, at section 3.14, JA8187; Brittain Dir., 310(18)-314(1), JA3948-52.

By misuse of this virtual line feature Plaintiffs virtually transformed large "conventional" granules into smaller "fine" granules prior to conducting average particle diameter measurements. Brittain Dir., 293(19)-297(5), JA3931-35. Although Plaintiffs argued that the specification required the granules to be spherical based on a precatory statement in the specification ("a fine granule being in the form of a rough sphere may be obtained" (emphasis added)), Bugay Dir. 81(15)-82(2), JA3719-20, something clearly not mandated by the specification, Plaintiffs' in effect urged that virtually dissected granules that did not have "curved surfaces" still be used in their analyses of average particle diameter.

Plaintiffs' dissection of hard agglomerates into smaller particles directly contradicts the practice of particle size determination by microscopy as taught in USP <776>, *see*, PTX 68, JA8339-44, and laser diffraction measurements according to USP <429> standards. *See*, DTX 45 at pg. 4 of 9, JA8243. Indeed, "a person of skill in particle sizing technology would know that it's never, under any

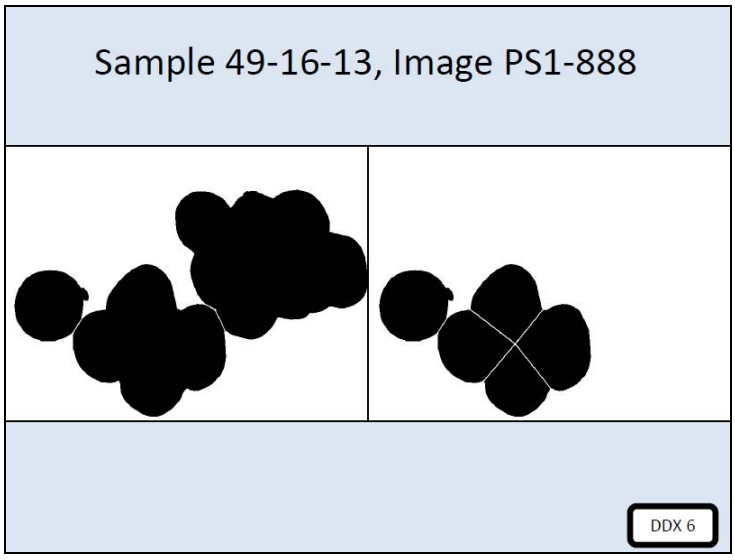
circumstance, appropriate to take a hard agglomerate and cut it into smaller pieces." Brittain Dir., 313(13-20), JA3951.

The drawing of "virtual" lines to artificially separate hard agglomerates was performed manually and was highly subjective. *See*, Brittain Dir., 293(24)-295(5), JA3931-35; Bugay Cross, 162(1-4), JA3800. Plaintiffs performed this same division of hard agglomerates on approximately twenty percent (20%) of the granules isolated from Zydus's exhibit batch tablets, creating multiple fictitious "computer-generated" small granules from real world existing much larger granules. Bugay Dir., 120(20-24), JA3758. As demonstrated in DDX 5 below which is an actual image of Zydus granules as seen by the operator of the optical microscope, the virtual division of hard agglomerates caused the software to treat the larger granules extracted from Zydus's exhibit batch tablets (shown on the left side of the exhibit) as multiple smaller granules (shown on the right side of the exhibit with lines drawn on the images), thereby skewing the average particle diameter measurement downward:



Brittain Dir., 297(6)-298(2), JA3935-36.

In some cases hard agglomerates were not even virtually transformed into smaller granules but were instead removed entirely from the calculation (compare images from DDX 6 below evidencing the removal of a hard agglomerate extracted from Zydus's exhibit batch tablets from the D_{50} determination). *See*, Brittain Dir., 299(3)-302(14), JA3937-40.



In a majority of cases, eggplant-shaped granules, comprising what appeared to be two cores, were artificially divided, even though such a shape is defined as being "spherical" in the specification. DTX 2 at col. 5, lines 40-42, JA5614.

The district court found that "to obtain the volume-based D_{50} of the "fine granules" in Zydus's ANDA product, Dr. Bugay used the standard deagglomeration feature included in the image analysis software accompanying his CILAS optical microscope." Opinion, at 20, JA0077. The district court did not find that Plaintiffs used the deagglomeration feature for its intended purpose. The evidence clearly shows that in this case the deagglomeration feature, which is intended to allow the operator to separate granules that are simply touching, was misued for the sole purpose of bringing a non-infringing product within the scope of claim 1 as construed.

D. The True Measurements of the Granular Ensembles Obtained By Plaintiffs From Zydus's Exhibit Batch Tablets Conclusively Demonstrate That Zydus's Proposed ANDA Product Does Not Infringe

The effect of Plaintiffs' virtual dissection of hard agglomerates and replacement with multiple smaller granules is aptly demonstrated in Defendants' Trial Exhibit 73. Plaintiffs extracted granules from Zydus's 2009 exhibit batch tablets and conducted two measurements using optical microscopy. The first measurement determined the D_{50} of the actual granular ensembles detected under the microscope, or what Plaintiffs referred to as "uncut" data, *i.e.*, the real world

size of the extracted granules without virtual computer generated "cutting" of hard agglomerates. The second measurement determined the D_{50} of what Plaintiffs referred to as "cut" data, *i.e.*, hard agglomerates transformed into multiple smaller granules by an operator placing one or more virtual lines to cause the software to treat the single hard agglomerate as multiple smaller granules:

Zydus 30-mg ANDA ODT Batch No: EMJ 352 (Mfg. Date: July – 2009)				
	Data Compiled From Plaintiffs' Exhibit 212		Data Compiled From Defendants' Exhibit 34	
Sample	Number of Granules Counted	Median Diameter (d_{50}) (µm)	Number of Granules Counted	Median Diameter (d_{50}) (µm)
49-16-3	5098	413.00	4275	457.1
49-21-4	5994	413.75	5145	446.5
49-22-2	6083	411.54	5208	443.4
49-22-4	6098	410.81	5207	444.0
Average Value =	5818	412.28	4959	447.8

DEFENDANTS' TRIAL EXHIBIT DTX 073

As DTX 73 conclusively demonstrates, the average particle diameter of the "uncut" granular ensembles (the column headed "Data Compiled from Plaintiffs' Exhibit 34") for each of the four tablets from which granules were extracted is above 440 µm, and does not infringe claim 1 as construed. It is only by subjectively drawing virtual lines to separate the large hard agglomerates into multiple smaller granules that Plaintiffs were able to place Zydus's exhibit batch tablets within the scope of claim 1 (the column headed "Data Compiled From

Plaintiffs' Exhibit 212"). As DTX 73 also demonstrates, Plaintiffs' virtual dissection of hard agglomerates added an average of 857 virtual granules to the number of granules counted, granules that did not physically exist.

Plaintiffs subsequently received a second batch of Zydus exhibit batch tablets manufactured in the Spring of 2012. Brittain Dir., 309(1-8), JA3947. Plaintiffs conducted the same analysis on granules extracted from those tablets, except that Plaintiffs only reported the D_{50} of the granules after virtually "cutting" hard agglomerates. Brittain Dir., 309(1-15), JA3947. Plaintiffs did not report the D_{50} of the actual granules extracted from the 2012 exhibit batch tablets, *i.e.*, the "uncut" data," as they had done with the 2009 exhibit batch tablets. *See*, Bugay Cross, 148(13-21), JA3786; Brittain Dir., 309(1-15), JA3947. Dr. Brittain opined that based on the increase in the average particle diameter of the "cut" data for the 2012 exhibit batch tablets when compared to the 2009 exhibit batch tablets "cut" data, the average particle diameter of the real world granules from the 2012 exhibit batch tablets would not infringe claim 1 as construed. Brittain Dir., 309(16)-310(10), JA3947-48. Plaintiffs introduced no evidence of the D_{50} of granules extracted from Zydus's exhibit batch tablets, either 2009 or 2012, using laser diffraction. Laser diffraction would have measured all of the granules present in the distribution and reported the true non-infringing D_{50}, not the D_{50} of virtually dissected, non-existing granules.

[redacted]

Following the district court's denial of Defendants' motion for reconsideration of the district court's claim construction ruling, D.I. 130, [redacted]

[redacted] Defendants utilized a static sampling methodology to obtain granule samples for purposes of conducting

particle size measurements. Opinion, at 23, JA0080. Dr. Brittain's unrebutted testimony demonstrated that static sampling is the norm in the pharmaceutical industry because of restraints placed on sampling by the FDA. Brittain Dir., 335(17)-336(13), JA3973-74.

[redacted] Defendants' sampling protocol thus provides a representative sample of granules for purposes of determining average particle diameter [redacted] *See*, Brittain Dir., 335(10)-336(13), JA3973-74.

[redacted]

[redacted]

IX
DEFENDANTS' CLEAR AND CONVINCING EVIDENCE OF INVALIDITY

A. The POSITA Would Know of A Number of Methodologies that Could be Used to Determine Average Particle Diameter of Granules Described in the '994 Patent, Each of Which Would Give a Different Numerical Result

The POSITA would know of a number of different methods that could potentially be used to measure granules of the size identified in the '994 Patent to determine average particle diameter, including: laser diffraction, optical microscopy, sieving, coulter counter, and light obscuration. Meyer-Stout Dir., 434(3-11), JA4072; Byrn Cross 540(8-12), JA4178. The POSITA would know that each of the many methods available for measuring average particle diameter will provide distinctly different numerical results when applied to the study of the same sample. Meyer-Stout Dir., 445(1)-448(4), JA4083-86. As a result, the same sample could be either infringing or non-infringing depending on the measurement technique used. *Id.*; Byrn Cross, 556(11-14), JA4194. The POSITA could not determine the scope of the '994 Patent's claims, or whether his invention infringes those claims, without specificity as to the measurement methodology to be used. See, Meyer-Stout Dir., 447(10)-448(4), JA4085-86.

B. The '994 Patent Fails To Provide A Written Description Sufficient to Teach One of Ordinary Skill In The Art The Effect of The Wide Variations In Compressions Associated With The Related Broad Hardness Strength of Claim 1 on Average Particle Diameter

Claim 1 of the '994 Patent claims "fine granules" having an average particle diameter of 400 μm or less post tableting, DTX 2, at claim 1, JA5630, but the specification only teaches determination of average particle diameter of granules pre-compression, or pre-tableting. DTX 2, at Examples 2-9, JA5622-30; Meyer-Stout Dir., 455(3-5), JA4093. Plaintiffs contended that the infringement determination can be made either pre-compression or post-compression, even though a POSITA would not know whether the granular ensemble is changed upon compression from a non-infringing pre-compression ensemble to an infringing post-compression ensemble. Byrn Cross, 550(25)-551(6), JA4188-89. Claim 1 allows for dramatically different compressions in specifying hardness strength over the very broad range of "about 1 to about 20kg." *See*, DTX 2, at claim 1, JA5630. The '994 Patent does not teach the effects of compression on average particle diameter, or the proper hardness strength for the orally disintegrable tablet so that the average particle diameter of the granular ensemble is the same pre-tableting and post-tableting. *See* Meyer-Stout Dir., 455(6-13), JA4093. The '994 Patent also does not teach how to measure granules from the compressed tablets to ensure that the average particle diameter of the extracted granular ensemble relates to the

average particle diameter of the pre-compressed granular ensemble, the only ensemble taught in the specification.

C. The Court's Claim Construction Makes Claim 1 Indefinite and Not Enabled

The "400 μm (± 10%)" deviation provided by the Court would be understood by a POSITA to create a range of 360 μm to 440 μm. *See*, Brittain Dir., 327(9)-328(23), JA3965-66. A POSITA would understand by "+/-" that there is just as much of a chance of falling in the plus part as there is of falling in the minus, or the negative part, of the range. *See*, *Id.* The POSITA would not read the minus out of "400 μm (± 10%)" and would not know whether the claim ceiling is 360 μm (400 μm -10%), 440 μm (400 μm + 10%) or some value in between 360 μm and 440 μm. Brittain Dir., 327(9)-328(12), JA3965-66. It would also read onto defined "conventional" granules.

X
SUMMARY OF THE ARGUMENT

The district court's judgment should be reversed, the corresponding injunction vacated, and judgment should enter in Defendants' favor on all asserted claims and counterclaims for a multitude of reasons.

First, the district court's construction of the claim term "fine granules having an average particle diameter of 400 μm or less" to mean "fine granules up to and including the enteric coating layer having an average particle diameter of 400 μm

(± 10%) or less" ignores the most fundamental tenant of claim construction and relies on extrinsic evidence even though the intrinsic evidence provides direct and conclusive support for the meaning of the disputed claim term. The intrinsic evidence clearly demonstrates that "fine granules having an average particle diameter of 400 μm or less" creates a ceiling at 400 μm as granular ensembles with average particle diameters of greater than 400 μm result in a feeling of roughness in the mouth, the very problem the invention is intended to solve. This fact is clearly supported by a disavowal made by the Patentee in one of its continuation applications of the '994 Patent family. *See*, DTX 9, at JA7228.

The district court's infringement finding is clearly erroneous as it is built upon the false premise that the '994 Patent requires hard agglomerates to be virtually deagglomerated during the measurement process so that only granules with single cores are measured in the determination of average particle diameter. The evidence demonstrated that the fluid-bed coating process utilized to manufacture granules makes the formation of hard agglomerates inevitable and the specification and file history make clear that the inventors measured all of the "obtained" granules after they were coated and sieved using a measurement technique that does not distinguish between hard agglomerates and granules with single cores.

The district court concluded that laser diffraction is only appropriate when the sample to be measured contains a "nominal" amount of hard agglomerates. However, there was no evidence presented as to what "nominal" means, what constitutes a "nominal" amount of hard agglomerates, the amount of hard agglomerates in the relevant exemplary granule batches of the specification, or how the POSITA would know whether the amount of hard agglomerates in a given sample was "nominal" or more than "nominal."

A statement by Plaintiffs' counsel during her opening statement that Plaintiffs' commercial product contains a "nominal" amount of hard agglomerates is not evidence, and is irrelevant in any case, as Plaintiffs' commercial product did not even exist when the application leading to the issuance of the '994 Patent was filed in 1999. Plaintiffs presented no evidence regarding the amount of hard agglomerates in the exemplary granule batches of the specification, facts necessary for the district court's ruling as to the appropriate use of laser diffraction for particle size determination by Zydus.

Even if optical microscopy is an appropriate measurement technique, Plaintiffs misused that technique in this case. Plaintiffs dissected hard agglomerates in a highly subjective manner with the specific intent of bringing Zydus's proposed ANDA product within the scope of claim 1 as construed in direct contradiction to the software package that does not allow its use for such

purpose. *See*, DTX 35, JA8187. Indeed, when Plaintiffs measured the actual granules extracted from Zydus's exhibit batch tablets the average particle diameter was in a non-infringing range. Measuring anything other than the actual granules as they exist is nonsensical inasmuch as the stated purpose of the invention is to create an orally disintegrable tablet with a "fine" granular ensemble that will not cause a feeling of roughness in the mouth. The only way to determine whether a given granule ensemble will cause a feeling of roughness in the mouth is to measure the actual granules, not virtually dissected pixelated images of the granules.

The district court's finding [redacted] is also clearly erroneous. Zydus determines the average particle diameter of granular ensembles in the same way and with the same methodology as the '994 Patent inventors. Defendants did not deagglomerate hard agglomerates prior to conducting measurements as there is nothing in the '994 Patent or its file history even suggesting that such a procedure should be used. Nor is there anything in the '994 Patent or file history that suggests only dynamic sampling could be utilized in making measurements.

Claim 1 is invalid regardless of whether the District Court's claim construction is applied.

First, the claim construction makes the claim not enabled as it brings within the scope of the claim the disparaged "conventional" granules, those with an average particle diameter of 400 μm or more, that cause the undesired feeling of roughness in the mouth. Indeed, the district court's claim construction effectively changes the '994 Patent's express definition of "fine" granules such that "fine" granules now include granules that do cause the undesired feeling of roughness in the mouth thereby defeating the very essence of the invention.

Second, the '994 Patent is also not enabled as it leaves open the possibility of the use of a number of known techniques for the determination of average particle diameter of enteric coated granules of the size identified in the '994 Patent some of which would indicate infringement, while others would not. These different analytical techniques for average particle diameter determination each measure different physical aspects of a granule. Each method would, therefore, give a different numerical value such that measurements conducted with one methodology could result in a granular ensemble being in a non-infringing range while measurements with a second methodology could result in that same sample being in an infringing range.

Third, the '994 Patent lacks written description. The inventors measured granular ensembles to determine average particle diameter pre-tableting, but claim 1 asserts a granular ensemble in the finished orally disintegrable tablet having an

average particle diameter of 400 μm or less. Plaintiffs contend that the infringement determination can be made either pre-tableting or post-tableting but the '994 Patent does not teach the POSITA how to ensure that average particle diameter is not altered pre-tableting to post-tableting, and Plaintiffs' expert admitted that infringement might be found post tableting but not pre-tableting and vice versa. Byrn Cross, at 552(10-17), JA4190.

Lastly, the district court's claim construction, advocated for by Plaintiffs, makes the claim indefinite as it creates a range of potential lines of demarcation for the determination of infringement between 360 μm and 440 μm and the POSITA is left to guess as to where the line of demarcation lies. It also allows for claim 1 to reach admitted prior art granular ensembles, explicitly defined as "conventional" in the specification.

XI
ARGUMENT

A. The Standard of Review

"This court reviews judgments of the district court after a bench trial 'for errors of law and clearly erroneous findings of fact." *Pozen, Inc. v. Par Pharma, Inc.*, 696 F.3d 1151, 1160 (Fed. Cir. 2012) (citation omitted). The district court's finding of infringement is reviewed under the clearly erroneous standard. *Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc.*, 467 F.3d 1370, 1375 (Fed. Cir. 2006). "A finding is 'clearly erroneous' when although there is evidence to

support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *Id.*, quoting *U.S. v. U.S. Gypsum*, 333 U.S. 364, 395 (1948). Likewise, the district court's finding that Defendants' failed to prove that the '994 Patent is invalid for lack of written description pursuant to 35 U.S.C. § 112, ¶ 1 is a question of fact that is reviewed for clear error. *Pozen, Inc.*, 696 F.3d, at 1166 (citation omitted). The district court's finding that Defendants failed to prove that the '994 Patent is not enabled pursuant to 35 U.S.C. § 112, ¶ 2, is reviewed *de novo*. *CFMT, Inc. v. Yieldup Intern'l. Corp.*, 349 F.3d 1333, 1337 (Fed. Cir. 2003). The district court's rulings on indefiniteness and claim construction are also reviewed *de novo*. *eplus, Inc. v. Lawson Software, Inc.*, 700 F.3d 509, 516 (Fed. Cir. 2013); *Biogen Idec, Inc. v. Glaxosmithkline LLC*, 713 F.3d 1090, 1094 (Fed. Cir. 2013).[4]

[4] This Court recently granted *en banc* review in *Lighting Ballast Control LLC v. Phillips Electronics N.A. Corp.*, 500 Fed.Appx. 951, 2013 WL 1035092 (Fed. Cir., March 15, 2013) on the issue of whether "this court should afford deference to any aspect of a district court's claim construction." *Id.* Until this Court decides otherwise, the standard of review of district court claim construction rulings is *de novo*.

B. The District Court's Claim Construction Ignores the Overwhelming Intrinsic Evidence in the Specification and File History and Instead Relies on Extrinsic Evidence that Postdates the Application Leading to the '994 Patent by More Than Five Years

It is axiomatic that "[t]he best source for understanding a technical term is the specification from which it arose, informed, as needed, by the prosecution history. . . . It is therefore entirely appropriate for a court, when conducting claim construction to rely heavily on the [specification] for guidance as to the meaning of the claims." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316-17 (Fed. Cir. 2005) *(en banc)* (citations omitted). Here, the district court ignored this axiom, and the direct language of the specification, and instead relied on extrinsic evidence that did not even exist at the time that the application leading to the '994 Patent was filed, or even when it issued. There was no reason for the district court to even consider this extrinsic evidence as the intrinsic evidence unquestionably provides the proper construction for the claim term.

The specification draws a bright line at 400 μm between "fine" granules, those that do not produce a feeling of roughness in the mouth, and "conventional" granules, those that do produce a feeling of roughness in the mouth. Brittain Dir., 288(6)-289(6), JA3926-27. The specification's reference to "fine" granules having an "average particle diameter of about 400 μm or less, in order that roughness is not felt in the mouth," DTX 2, at col 5, lns. 57-64, JA5614 (emphasis added), does

not alter this conclusion. Indeed, the term "about" does not precede the term "400 μm or less" throughout the specification and, significantly, the specification enumerates that the preferred average particle diameter is actually less than 400 μm, providing context for the "about" modifier used in respect of a specified phrase not found *in toto* in the claim at issue. *See*, DTX 2, col. 2, lns. 20-22, JA5612; DTX 2, col. 5, lns. 63-64, JA5614; and DTX 2, col. 12, lns. 58-61, JA5617. Thus, the intrinsic evidence conclusively demonstrates that the word "about" connotes downward movement from 400 μm, as granules with average particles diameters above 400 μm cause roughness in the mouth. The file history of a continuation application of the '994 Patent further makes clear that the Patentees never intended for "less than 400 μm" to include average particle diameter measurement of granular ensembles above 400 μm, but instead intended for them to be "within" 400 μm. *See*, DTX 9, at JA7228.

Even if extrinsic evidence was necessary in this case, which it was not, the extrinsic evidence relied upon by the district court was published in 2004 (USP <429>, Light Diffraction Measurement of Particle Size,) and 2007 (PQRI Recommendations on Particle-Size Analysis of Drug Substances Used in Oral Dosage Forms)(Byrn Decl., at Exs. 5 and 6, introduced at trial as DTX 45 and 47, JA8240-66), while the application leading to the '994 Patent was filed in 1999 and the '994 Patent issued on December 11, 2001. Obviously the POSITA could not

rely on references that did not exist to ascertain the meaning of a claim term. *See Innova/PureWater, Inc. v. Safari Water Filtrations Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004) ("A court construing a patent claim seeks to accord a claim the meaning it would have . . . at the time of the invention.").

The district court was fully aware that the references relied upon by Plaintiffs substantially postdated the filing of the application and issuance of the '994 Patent as Defendants specifically highlighted this fact and introduced a more contemporaneous reference. *See*, Defendants' Responsive Claim Construction Brief, [D.I. 80], at 8-11, JA0823-26. Defendants also highlighted the fact that the USP reference relied upon by Plaintiffs as support for their claim construction relates to "large vat" bulk sampling errors using laser diffraction. *See*, *Markman* Tran., at 36(17)-37(6), JA1290-91. That reference is wholly irrelevant to the issue of measurements of all of the granules extracted from the small volume of a finished tablet, the very matter at issue in this case. Despite the multiple problems with Plaintiffs extrinsic evidence specifically highlighted by Defendants, the district court relied on those references in construing the claim term at issue.

Whether based on the intrinsic evidence or the extrinsic evidence, the district court's claim construction cannot stand. The proper construction for the claim term "fine granules having an average particle diameter of 400 μm or less" is "fine granules having an average particle diameter of precisely 400 μm or less," using

"precisely" in its scientific meaning to include small instrument errors. When this proper construction is applied to the facts of this case Zydus's proposed ANDA product does not infringe claim 1 of the '994 Patent, regardless of the measurement methodology used and whether hard agglomerates are virtually deagglomerated. Thus, the judgment of infringement and corresponding injunction should be vacated and judgment of noninfringement should be entered in Zydus's favor. *See Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1328 (Fed. Cir. 2002) ("[W]hen we determine on appeal, as a matter of law, that a trial judge has misinterpreted a patent claim, we independently construe the claim term to determine its correct meaning, and then determine if the facts presented at trial can support the appealed judgment.") (citation omitted).

C. The District Court's Infringement Finding is Clearly Erroneous

1. The District Court's Finding of Infringement is Not Supported by the Record and Completely Ignores the Specification

Findings of fact made by the trier of fact must be supported by record evidence, and a determination of infringement made following a bench trial will be overturned when the infringement determination is clearly erroneous. *See Abraxis Bioscience, Inc.*, 467 F.3d 1370, at 1375. Here, the district court's infringement determination is clearly erroneous because it is premised upon certain core factual findings that are simply not supported by the record.

The district court's clearly erroneous finding of infringement is built upon the faulty assumption that the determination of average particle diameter is to be limited to granules containing single cores, and as a result hard agglomerate granules must be virtually deagglomerated. *See*, Opinion, at 11-12, JA0068-69. Single cores are the starting point for the manufacture of granules, but they are not what is measured. It is only after the individual cores have gone through the fluid-bed coating process, a process that inevitably creates hard agglomerates, that measurements are conducted on the obtained granules.

The '994 Patent does not teach, discuss, or even mention deagglomeration, virtual or otherwise, a fact that makes eminent sense because the inventors used laser diffraction to measure particle size and both parties' experts agreed it cannot distinguish between hard agglomerate granules and granules containing a single core. Plaintiffs suggested that the POSITA would know to deagglomerate and to utilize a measurement methodology other than laser diffraction when a sample contains more than a "nominal" amount of hard agglomerates. Plaintiffs offered no evidence whatsoever as to the agglomerate content of the exemplary granules of the '994 Patent, as to what constitutes a "nominal" amount of hard agglomerates, or how the POSITA would know when the amount of hard agglomerates present crossed over the undefined line from "nominal" to more than "nominal."

Plaintiffs' counsel's statement to the district court during opening statements that Plaintiffs' commercial product contains a nominal amount of hard agglomerates is not evidence. *See*, *e.g.*, *U.S. v. Sotomayor-Teijeiro*, Nos. 11-2600, 11-3147, 499 Fed.Appx. 151, 2012 WL 4497417 (3d Cir. Oct. 2, 2012). Even if it was evidence the statement is irrelevant as the issue is not the amount of hard agglomerates in Plaintiffs' commercial product, but the amount of agglomerates in the exemplary batches of the '994 Patent for which Plaintiffs offered no evidence.

Defendants, on the other hand, offered evidence demonstrating that in each of the examples of the '994 Patent the named inventors manufactured granules, sieved those granules, and then immediately measured the average particle diameter of the obtained granules using a laser diffraction method without undertaking any specific process to deagglomerate, whether via the use of computer software or otherwise. *See* DTX 2, at Examples 3-9, JA5623-30; DTX 7, at JA6139-44.

Defendants also introduced deposition testimony of '994 Patent inventor Toshihiro Shimizu who testified that the inventors sieved granules but did not perform any testing after the sieving step to determine whether granules, including hard agglomerates, that were larger than the largest sieve opening had gotten through the sieve. Nov. 15, 2011 deposition of Toshihiro Shimizu, at 133(10)-135(3), JA3349-51. Thus, the only reasonable inference to be drawn is that the

inventors included hard agglomerates created during the manufacturing process in the determination of average particle diameter. This inference is entirely consistent with Plaintiffs' stated position in their Infringement Contentions served in this case that all of the granules in Zydus's proposed ANDA product were "fine granules" of claim 1. DTX 30, at pg. 3, JA8158. When those same hard agglomerates are included in the determination of the average particle diameter of granules extracted from Zydus's exhibit batch tablets Zydus does not infringe the asserted claim as construed. *See*, DTX 73, JA8338.

The district court's infringement finding also ignores the very variance it permits in its claim construction. That is, the measurements relied on for infringement could also be off as much as 10%, which is in a non-infringing range.

2. The Inventive Concept of the Avoidance of Roughness in the Mouth Requires the Measurement of All Granules in the Form in Which They Actually Exist

The avoidance of roughness in the mouth is the inventive concept, a fact that was emphasized by Plaintiffs in obtaining their desired claim construction. *See* Brittain Dir., 321(24)-323(10), JA3959-61; *Markman* Tran., at 12(10-15), JA1266. The virtual deagglomeration procedure used by Plaintiffs does not physically alter the granular distribution the patient actually ingests and does not have any effect on whether such granular distribution would cause roughness in the mouth. Thus, the average particle diameter determination made by Plaintiffs following the

virtual deagglomeration procedure is not a true representation of the average particle diameter of the granules present, or whether those granules will cause a feeling of roughness in the mouth. The only way to determine the true average particle diameter of a given granular distribution is to measure all of the granules as they exist. This is exactly what the inventors did and exactly what Zydus did in designing around claim 1. *See Honeywell Intern.'l., Inc. v. ITT Industries, Inc.*, 452 F.3d 1312, 1318 (Fed. Cir. 2006) (noting that "[t]he public is entitled to take the patentee at his word" and rely on what the patentee refers to as "the invention").

3. The Conclusion that Virtual Deagglomeration is Required and Laser Diffraction is Not An Appropriate Measurement Technique Caused the District Court to Reject this Court's Precedent Concerning the Appropriate Infringement Analysis in the ANDA Context

"[C]ompetitors are entitled to review the public record, apply the established rules of claim construction, ascertain the scope of the patentee's claimed invention and, thus, design around the claimed invention." *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996). Zydus relied on the public record, ascertained the scope of the invention, and, relying on this Court's decision in *Bayer AG v. Elan*, [redacted]

Following trial the district court found that the infringement inquiry does not begin and end with the four corners of Zydus's ANDA. Opinion, at 21-24, JA0078-81. The district court's rejection of the rule announced in *Elan* is premised entirely on the district court's clearly erroneous findings that hard agglomerates must be deagglomerated prior to conducting measurements to determine average particle diameter, and that static sampling, something mandated by FDA safety issues in pharmaceutical manufacture, does not provide a representative sample of granules upon which to conduct measurements. The former finding is belied by the overwhelming evidence discussed at length herein showing that the '994 Patent inventors did not deagglomerate in reality or virtually hard agglomerates, but instead measured them using laser diffraction to determine the average particle diameter of the obtained granules. The finding on static sampling ignores the testimony of Dr. Brittain that Defendants are using a sampling protocol mandated by the confines of the FDA and that Zydus's specific static sampling protocol would provide a representative sample. Absent the district court's clearly erroneous underlying findings, the four corners of Zydus's ANDA resolves the issue of infringement in Zydus's favor as Zydus cannot legally market and sell a product that does not comply with its ANDA. *See Elan.*, at 1249-50.

The district found that the present case is more akin to *Bayer AG v. Biovail*, 279 F.3d 1340 (Fed. Cir. 2002) ("*Biovail*"), than *Elan*. Opinion, at 24, JA0081.

Biovail arises out of the same general set of operative facts as *Elan*, and involved claims of direct infringement by a product that Elan commercialized following this court's decision in *Elan*, and a hypothetical ANDA product that Elan sought to market and sell which was a 60 mg version of the product already on the market. *Biovail*, at 1346. *Elan* obtained summary judgment on the basis that Bayer was collaterally estopped from litigating the *Biovail* infringement issues based on *Elan*. *Id*. at 1342. This Court reversed the grant of summary judgment in Elan's favor and remanded the case to the district court for further proceedings, particularly claim construction proceedings. *Id.*, at 1350.

This case is nothing like *Biovail*. Plaintiffs do not claim to have uncovered additional evidence of infringement from Zydus's non-existing commercial product. Instead, Plaintiffs claim that the granules extracted from Zydus's exhibit batch tablets must be measured using optical microscopy after hard agglomerates are subjectively and virtually deagglomerated. Nothing even close to that issue was addressed in *Biovail*. The district court rejected *Elan* primarily because the district court accepted Plaintiffs multi-stepped, highly subjective measurement technique that has no support in the specification or file history, not because *Biovail* more closely resembles this case.

D. The District Court's Claim Construction, Which Was Advocated For By Plaintiffs, Clearly Invalidated the Claims

1. Contrary to this Court's Precedent, the District Court Unilaterally Changed Explicit Definitions in the Patent Specification to Support Its Clearly Erroneous Claim Construction

This Court has "repeatedly and consistently [ ] recognized that courts may not redraft claims, whether to make them operable or sustain their validity. Even a nonsensical result does not require the court to redraft the claims of the patent." *Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) ("It is the job of the patentee, and not the court, to write patents carefully and consistently. The court cannot rewrite the patent…"(citation omitted)). Even more so, a court cannot change an explicit inventor-chosen definition in a specification. Despite this rule, the district court rewrote the definitions of "fine" granules in the claim and "conventional" granules set forth in the specification, and then subsequently rewrote its own ±10% to read the minus out.

When faced with the ambiguity of Plaintiffs' own making, *i.e.* what the term "average particle diameter of 400 μm (± 10%) or less" actually means, the district court choose to ignore the minus component of the variance, selectively adopting the proposition of Dr. Bugay that a scientist would just ignore the minus component in the context of a maximum limit (just as Dr. Bugay stated he would ignore the minus component if a bank officer told him he had been approved for a

loan of X dollars ± 10%). Bugay Cross, 227(13-22), JA3865. The district court also adopted Plaintiffs' assertion that the definition of "conventional" granules in the specification could be rewritten to include the ± 10% variation. When doing so, the court once more selectively ignored the minus component of the ± 10%, even though this definition relates to average particle diameters of 400 μm or more. DTX 2, at col. 2, lns. 13-22, (emphasis added), JA5612. This selective correction of an adopted claim construction is contrary to law.

"Fine" granules are explicitly defined in the specification as not only avoiding the disparaged feeling of "roughness in the mouth, DTX 2, col. 5, lns. 57-64, JA5614, but also as having a maximum particle size of a diameter of "practically 425 μm or less" where "practically" is defined as allowing for a small quantity of "about 5 weight % or less" of particle diameters outside the range. DTX 2, at, col. 5, ln 65 – col. 6 ln 9, JA5614. *See Sinorgchem Co., Shandong v. Int'l Trade Comm'n*, 511 F.3d 1132, 1136 (Fed. Cir. 2007) (when a phrase "is set off by quotation marks [it is] a strong indication that what follows is a definition"). Moreover, as anyone of ordinary skill in particle size measurements would understand it is necessary to define a particle distribution or ensemble by not only its median but also by its maximum particle size inasmuch as a median by itself cannot define any particle distribution as it allows for an infinite number of possible permutations.

By ignoring explicit definitions in the specification and allowing for construction of "average particle diameter" of the granular distribution to reach 440 μm, the district court allowed for more than half of the granules to have a particle diameter above 440 μm, and thus more than 50% over 425 μm (the specified maximum particle size diameter in the specification, and significantly more than tenfold the 5 weight percent of the granules in the granular distribution allowed by the word "practically" before 425 μm). Thus the district court clearly invalidated the claim.

Moreso, the district court impermissibly changed the definition of "conventional" granules set forth at col. 2, ln. 12-22, to now read "440 μm or more of average particle diameter." This section of the specification defines such "conventional" granules as having "large particle diameters" which it defines as "(400 μm or more of average particle diameter)" and it explicitly disavows such conventional granular distributions as producing "a feeling of roughness in the mouth," and having inferior workability when dispensing and "difficulties in consistently adding a regular amount of the granules when they are combined into tablets and capsules." DTX 2, at col. 2, lns. 12-22, JA5612.

When a special definition is made in the specification, the inventor's lexicography governs, as it does when the specification reveals an intentional disclaimer. *See Phillips*, 415 F.3d at 1316, (citing *CCS Fitness, Inc. v. Brunswick*

Corp., 288 F.3d 1359, 1366 (Fed. Cir. 2002)); s*ee also Ekchian v. Home Depot, Inc*., 104 F.3d 1299, 1304 (Fed. Cir. 1997) ("[s]ince, by distinguishing the claimed invention over the prior art, an applicant is indicating what the claims do not cover, he is by implication surrendering such protection."). The court cannot alter explicit definitions in the specification that make clear that the invention does not include a particular feature. *See SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc*. 242 F.3d 1337, 1341 (Fed. Cir. 2001).[5] That is exactly what the district court's claim construction does in this case.

2. Plaintiff's Advocated for Claim Construction Results in a Mathematical Impossibility Wherein the Median Particle Diameter of the Ensemble May Be Greater Than the Stated Maximum Particle Diameter of Individual Granules in the Ensemble

The district court's claim construction also creates the mathematical impossibility where the median of a given set is above the stated maximum. The court's claim construction establishes a potential D_{50} in the range of 360 μm to 440 μm (400 μm ± 10%). *See*, Brittain Dir., 327(9)-328(23), JA3965-66. Plaintiffs argued, and the district court agreed, that the claim construction does not create a range because the POSITA would know to read the minus out of the construction

[5] Even under the doctrine of claim differentiation, a court cannot "alter a definition that is otherwise clear from the…description." *O.I. Corp. v. Tekmar Co., Inc*., 115 F.3d 1576, 1582 (Fed. Cir. 1997)

such that it would actually mean 440 μm or less. Opinion, at 42, JA0099. Assuming *arguendo* that the POSITA would simply ignore the minus, the claim as construed allows for the median (D_{50}) to be above the maximum allowed particle diameter of all granules in the granular distribution of "practically 425 μm or less", again, a mathematical impossibility. *See*, Brittain Dir., 326(2)-327(8), JA3964-65.

E. Irrespective of the District Court's Claim Construction Claim 1 is Invalid for Failure in Written Description Support. The District Court Misconstrued This Court's Failure in Written Description Holding in *Eli Lilly v. Teva Pharmaceuticals* to Suggest the Case Related to Situations Wherein a POSITA Would Not Understand How to Extract Granules From a Compressed Tablet

In *Eli Lilly & Co. v. Teva Pharms. USA, Inc.* ("*Teva*"), 619 F.3d 1329 (Fed. Cir. 2010), this Court upheld a district court's finding of invalidity for failure to comply with the written description requirement where the patent only disclosed the mean particle size of an ensemble of particles pre-compression, and yet the plaintiffs urged the claims could be infringed by non-infringing pre-compression ensembles of particles if the mean particle size changed once compressed into tablet form.

Claim 1 of the '994 Patent asserts a finished tablet that includes fine granules with an average particle diameter of 400 μm or less, but the specification only teaches measurements of granules pre-tableting, without relaying to a POSITA how to ensure that tableting compression forces in making the tablet (which could be extremely high given the recited hardness strength of the tablets specified in

claim 1) do not alter the average particle diameter of pre-tableted granular distributions. Meyer-Stout Dir., 455(3-13), JA4093. In this case, the parties' experts agreed that as a result of compression one could be found to be non-infringing pre-tableting while infringing post-tableting, or infringing pre-tableting while non-infringing post-tableting. *See* Byrn Cross at 552(10-17), JA4190; Meyer-Stout Dir., 453(22)-455(2), JA4091-93. This is not unexpected given the very wide range of hardness specified in Claim 1. *See*, Meyer-Stout Dir., at 451(4)-453(9), JA4089-91. Dr. Meyer-Stout testified that because of the complex physics of compression, the POSITA could not predict whether the D_{50} would increase or decrease of post tableting. Meyer-Stout Dir. 454(14)-455(2), JA4092-93. Defendants thus argued that *Teva*, wherein the plaintiff's own expert "conceded that [o]ne reading the [Particle Size Patent] in 1996 would not know whether the particle size was being increased or decreased [or remain the same] in the formulation," 619 F.3d, at 1345, was directly on point and mandated that judgment enter in Defendants' favor due to a failure of written description.

The district court adopted Plaintiffs misconstruction of this Court's *Teva* holding, finding that it applied only if a POSITA would not understand how to extract granules from a tablet post-compression to conduct measurements to determine average particle diameter. Opinion, at 40, JA0097. That finding is wholly unsupported by the *Teva* opinion. Indeed, under the precedent established

in *Teva*, a patent is invalid for failing to satisfy the written description requirement where, as here, the specification is directed to granules with a certain average particle diameter pre-compression and a POSITA understands that compressional forces on the tablet might allow for infringing ensembles to form from non-infringing pre-compression particle ensembles. *Teva*, at 1344-45. Indeed, Plaintiffs' expert agreed that a granular ensemble could be non-infringing pre-compression but infringing post- compression, and vice versa, such that compression would have turned a non-infringing granular ensemble into an infringing ensemble. Byrn Dir., 552(10-17), JA4190.

F. Irrespective of the Courts' Claim Construction, Claim 1 is Invalid As Under this Court's Precedent Plaintiffs' Expert's Testimony That the Claim Allowed for Multiple Measurement Methodologies to Determine Average Particle Diameter Which Could Give a Different Result Such that One Methodology Could Show a Sample to be in an Infringing Range While Another Methodology Could Show that Same Sample was ***Non-Infringing***

In *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003) this Court found a claim directed to determining whether a glycoprotein had "glycosylation which differs from that of human urinary erythropoetin" to be invalid for failure to satisfy 35 U.S.C. § 112 for failing to "direct those of ordinary skill in the art to a standard by which the appropriate comparison can be made." 314 F.3d at 1341. In *Amgen*, the plaintiff urged that the claim allowed for any standard prior art technique known as of 1983-84 to be used in determination of

glycosylation and the specification itself failed to limit such tests to any measurement methods. This Court found that as infringement could depend on what methodology of measurement was chosen, that the patentee had failed in drafting the claim in a manner "to permit a potential competitor to determine whether or not he is infringing." *Id.* at 1342 (citing *Morton Int'l, Inc. v. Cardinal Chem Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993),[6] and thus that the claim was invalid as not enabled.

In this case, the record evidence demonstrates that a POSITA, like the ordinary artisan in the *Amgen* and *Honeywell Intern'l* cases, could never know whether they were infringing the claims of the '994 Patent as one measurement methodology (such as laser diffraction) could provide an average particle diameter result that was in a non-infringing range and another methodology could provide an average particle diameter result for the same sample that is in an infringing range, even if both measurements could be said to be "correct" under the

[6] *See also Honeywell Intern'l., Inc. v. Intern'l. Trade Comm'n*, 341 F.3d 1332, 1340 (Fed. Cir. 2003) (finding the claims of a patent invalid based on asserted multiple methods for determining infringement because "the sample preparation method is critical to discerning whether [the product at issue] has been produced by the claimed process, [and] knowing the proper sample preparation method is necessary to practice the invention.").

constraints of the methodology. Meyer-Stout Dir., 445(1)-448(4), JA4083-86; Byrn Dir., 510(25)-511(5), JA4148-49.

Zydus's expert, Dr. Meyer-Stout, also testified based on her 30 years of experience using a method asserted by the Plaintiffs to be encompassed by claim 1, *i.e.*, coulter counter, *see* Byrn Cross 540(8-12), JA4178, that she did not know whether the technique could be used given the breadth of the claim and even if it could be used in some limited instance, its application would require undue experimentation. *See*, Meyer-Stout Dir., 448(5)-449(11), JA4086-87. Although her testimony on this point was unrebutted, the district court rejected Dr. Meyer-Stout's opinion regarding coulter-counter because she did not perform experiments to demonstrate that the technique couldn't be applied for the entire breadth of the claim, something she implicitly stated could not be done. *See, Id.*, JA4086-87; Opinion, at 28-30, JA0085-87.

XII
CONCLUSION AND RELIEF SOUGHT

For all of the foregoing reasons, the district court's judgment entered in Plaintiffs' favor should be reversed in all respects and the district court should be directed to enter judgment in favor of Zydus on Plaintiffs' infringement claim and in favor of Defendants on their counterclaims for noninfringement and invalidity. In addition, the injunction entered against Zydus prohibiting it from "engaging in the commercial manufacture, use, offer for sale or sale within the United States, or

importation into the United States, of Zydus's proposed ANDA product until the expiration of the '994 Patent" should be vacated so that Zydus can begin marketing and selling its non-infringing ANDA product upon receipt of FDA approval.

Dated: July 15, 2013

Respectfully submitted,

By: /s/ *Steven J. Moore*

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PARTIES REPRESENTED

ZYDUS PHARMACEUTICALS USA INC.

CADILA HEALTHCARE LIMITED

PROOF OF SERVICE

The undersigned hereby certifies that on July 15, 2013, true copies of the foregoing document were served on all parties or their counsel of record through this Court's CM/ECF system and via email.

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Dated: July 15, 2013

/s/ *Steven J. Moore*
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CERTIFICATE OF INTEREST

Counsel for Defendants-Appellants certifies the following:

1. The full name of every party or amicus represented by me is:

Zydus Pharmaceuticals USA, Inc. and Cadila Healthcare Limited.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

N/A.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are: N/A.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or are expected to appear in this court are:

KELLEY DRYE & WARREN LLP; Joseph A. Boyle, Vincent P. Rao, Steven J. Moore, James E. Nealon, and James M. Moriarty.

Dated: July 15, 2013

By: */s/ Steven J. Moore*

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Form 19

FORM 19. Certificate of Compliance With Rule 32(a)

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

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/s/ Steven J. Moore

(Signature of Attorney)

Steven J. Moore

(Name of Attorney)

Attorney for Defendants-Appellants

(State whether representing appellant, appellee, etc.)

July 15, 2013

(Date)

Reset Fields

ADDENDUM 1

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL CO, LIMITED, et al. Plaintiff, v. ZYDUS PHARMACEUTICALS USA INC., et al. Defendant.	Civil Action No. 10-1723 (JAP) **JUDGMENT**

This is an action for patent infringement brought by Plaintiffs Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals North America, Inc., Takeda Pharmaceuticals LLC, and Takeda Pharmaceuticals America, Inc. (collectively "Takeda" or "Plaintiffs") against Zydus Pharmaceuticals (USA) Inc. ("Zydus") and Cadila Healthcare Limited ("Cadila") (collectively or "Defendants") pursuant to the Hatch-Waxman Act, 21 U.S.C. § 355(j), alleging infringement of United States Patent Nos. 6,328,994 (the "'994 patent"). A bench trial was held March 26 to April 1, 2013. For the reasons in the accompanying Opinion,

IT IS on this 7th day of May 2013

ORDERED as follows:

1. Judgment is entered in favor of Takeda against Zydus on Takeda's claim of infringement of claim 1 of the '994 patent.

2. Judgment is entered in favor of Takeda on Defendants' counterclaims seeking declarations of noninfringement and invalidity of the '994 patent.

3. The effective date of any Food and Drug Administration approval of Zydus's ANDA product that is the subject of this lawsuit shall be no earlier than the date of expiration for '994 patent and any pediatric exclusivity that applies to the '994 patent.

4. Zydus is hereby enjoined from engaging in the commercial manufacture, use, offer for sale or sale within the United States, or importation into the United States, of Zydus's ANDA product until expiration of the '994 patent.

/s/ Joel A. Pisano
JOEL A. PISANO, U.S.D.J.

ADDENDUM 2

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL CO, LIMITED, et al. Plaintiff, v. ZYDUS PHARMACEUTICALS USA INC., et al. Defendant.	Civil Action No. 10-1723 (JAP) **OPINION** FILED UNDER TEMPORARY SEAL

PISANO, District Judge.

This is an action for patent infringement brought by Plaintiffs Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals North America, Inc., Takeda Pharmaceuticals LLC, and Takeda Pharmaceuticals America, Inc. (collectively "Takeda" or "Plaintiffs") against Zydus Pharmaceuticals (USA) Inc. ("Zydus") and Cadila Healthcare Limited ("Cadila") (collectively or "Defendants") pursuant to the Hatch-Waxman Act, 21 U.S.C. § 355(j). Plaintiffs bring this action in response to the filing by Zydus of an abbreviated new drug application with the U.S. Food and Drug Administration ("FDA") seeking approval to market and sell a generic version of Plaintiffs' drug product, Prevacid SoluTab. A four-day bench trial was held from March 26 to April 1, 2013, and this Opinion constitutes the Court's findings of fact and conclusions of law. After careful consideration of the record before it, the Court finds in favor of Plaintiffs.

I. BACKGROUND

A. The Parties[1]

Plaintiff Takeda Pharmaceutical Company Limited ("Takeda Japan") is a Japanese corporation, having a principal place of business at 1-1, Doshomachi 4-chome, Chuoku, Osaka, Japan. Amended Complaint (D.I.[2] 98) ¶ 1. Takeda Japan is involved in the research, development, and marketing of pharmaceutical products. *Id.*

Plaintiff Takeda Pharmaceuticals North America, Inc. ("TPNA") is a Delaware corporation, having a principal place of business at One Takeda Parkway, Deerfield, Illinois 60015. *Id.* ¶ 2. As part of its business, TPNA is involved in the research, development, and marketing of pharmaceutical products. TPNA has the exclusive right to import lansoprazole orally disintegrating tablets and to sell them to Takeda Pharmaceuticals LLC. *Id.*

Plaintiff Takeda Pharmaceuticals LLC ("Takeda LLC") is a Delaware limited liability company, having a principal place of business at One Takeda Parkway, Deerfield, Illinois 60015. *Id.* ¶3. Takeda LLC is involved in the purchase and sale of pharmaceutical products. Takeda LLC is the exclusive licensee of the patent-in-suit, U.S. Patent No. 6,328,994 ("the '994 Patent"). *Id.*

Plaintiff Takeda Pharmaceuticals America, Inc. ("Takeda America") is a Delaware corporation, having a principal place of business at One Takeda Parkway, Deerfield, Illinois 60015. *Id.* ¶ 4. Takeda America is involved in the purchase, sale and marketing of pharmaceutical products. Takeda America has the exclusive right to sell lansoprazole orally-disintegrating tablets to the public under the patents. *Id.*

[1] Ethypharm, S.A., a named plaintiff, sought relief in this action solely with respect to U.S. Patent No. 5,464,632. All claims relating to this patent were resolved, however, prior to trial.
[2] To reference entries on the Court's docket, the abbreviation "D.I." (docket index) is used.

Defendant Zydus Pharmaceuticals USA Inc. ("Zydus") is a pharmaceutical company primarily engaged in the sale of generic pharmaceutical products. Amended Complaint ¶ 6.

Defendant Cadila Healthcare Limited ("Cadila") is a pharmaceutical company primarily engaged in the business of researching, developing, and manufacturing pharmaceutical products. Amended Complaint ¶ 7.[3]

B. The ANDA Filing

On or about February 19, 2010, Zydus sent a letter to Plaintiffs (the "Notice Letter") informing Plaintiffs that Zydus had filed abbreviated new drug application ("ANDA") No. 200816 with the FDA seeking approval to market and sell a generic version of Plaintiffs' Prevacid SoluTab ("Prevacid") product in 15 mg and 30 mg strengths. Amended Complaint, at ¶ 32; Answer, at ¶ 32. The Notice Letter included a Paragraph IV statement pursuant to 21 USC § 355(j)(2)(b) whereby Zydus informed Plaintiffs that, in Zydus's opinion, the Orange Book patents covering Prevacid were invalid and/or would not be infringed by Zydus's commercialization of the product described in its ANDA. Amended Complaint, at ¶ 32; Answer, at ¶ 32. This action followed.

C. The Patent-In-Suit

Originally, there were four patents at issue in this action: United States Patent Nos. 6,328,994 (the "'994 patent"), 7,431,942 (the "'942 patent"), 7,875,292 (the " '292 patent") and 5,464,632 (the " '632 patent"). The '632 patent expired on November 7, 2012. By agreement, the parties withdrew all claims and counterclaims related to the '632 patent, the '942 patent and the '292 patent prior to the commencement of trial. D.I. 327. Plaintiffs' also withdrew any claims of infringement of claim 2 of the '994 patent. Trial Transcript ("Tr.")

[3] Although named as a defendant in this action, Plaintiffs presented no evidence at trial regarding Cadila with respect to any of the allegations brought against Cadila in the complaint.

7:15-23. Thus, only claim 1 of the '994 patent remained at issue in this case at the start of trial.

The '994 patent is directed to lansoprazole orally disintegratable tablets. As stated above, Plaintiffs allege that Defendants infringe claim 1 of the '994 patent. Specifically, Plaintiffs contend that Defendants infringe the claim limitation of claim 1 related to the average particle diameter of fine granules in the claimed invention.

D. Witnesses At Trial

In its infringement case-in-chief, Takeda called Dr. Brian Fennerty and Dr. David E. Bugay. Dr. Bugay was proffered as an "expert in pharmaceutical formulation" and testified regarding infringement. Tr. 75:1-4; DTX 23. Dr. Fennerty, a Board certified gastroenterologist, was not proffered as an expert, and he testified about proton pump inhibitors ("PPIs"), Prevacid SoluTab, and orally disintegrating tablets ("ODTs"). See Tr. 44:19-22, 53:13-15, 55:14 to 56:4; DTX 22. Takeda also called Adam Zaeske, Vice President of Managed Markets and Trade for Takeda America and formerly the senior director of marketing for the gastrointestinal franchise for TPNA.[4] Mr. Zaeske's testimony was directed toward the harm that would be suffered by Takeda if Zydus were to launch their ANDA product.

Defendants proffered Dr. Harry Brittain as an expert witness in the areas of physical chemistry and the science of formulation. Tr. 256:24 to 257. Defendants also called Dr. Paula Meyer-Stout, an Associate Professor of Pharmaceutics at the University of West Virginia, Tr. at 430:21-431:3; DTX 17, who was proffered and accepted as an expert in the areas of pharmaceutical chemistry and industrial pharmacy. Tr. 433:6-10.

[4] Due to scheduling issues and with consent of Defendants, Plaintiffs called Mr. Zaeske out of order.

In rebuttal to Defendants' invalidity claims, Plaintiffs called Dr. Stephen Byrn, who was proffered and accepted as an expert in physical chemistry and the science of formulation. Tr. 477:6-9, DTX 25.

The parties also submitted the deposition testimony of a number of fact witnesses who were unavailable for trial.

E. Credibility Determinations

With respect to the witnesses appearing live at trial, the Court had the opportunity to hear their testimony and observe their demeanor. Having done so, the Court has made certain credibility determinations as well as determinations relating to the appropriate weight to accord various testimony. Such determinations are reflected the factual findings set forth in Opinion.

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

The Court has heard all witness testimony and considered the documentary evidence, and, as stated above, has accorded weight to the evidence as deemed appropriate. The parties having submitted their proposed findings of facts and conclusions of law, the Court finds that a preponderance of the evidence submitted supports the facts proposed by Plaintiffs.

A. The '994 Patent

The '994 patent is directed toward novel ODT formulations containing fine granules of enteric-coated acid-labile drug. *See* DTX 2 at Abstract. According to the patent specification, the fine granules in the novel ODT formulations have an average particle diameter of about 400 μm or less. DTX 2 at col. 5, ll. 57-63. The '994 patent also addresses difficulties in producing ODTs that contain an acid-labile active ingredient (*i.e.*, lansoprazole); acid-labile ingredients are susceptible to degradation in acidic environments.

Because the drug will degrade in the acidic environment of the stomach, formulations with an acid-labile active ingredient must be designed so that the active ingredient is not released as it passes through the stomach, but rather is released in the intestine. Tr. 55:3-13. The '994 patent teaches using an enteric-coated drug granule to achieve this result. DTX 2 at col. 2, ll. 25-30.

It is possible that tablet compaction may cause problems for enteric-coated drug granules. The pressure of the compression can cause the enteric coat to crack. Without an intact enteric coat, the drug can escape from the granule and release in the mouth, esophagus or stomach, instead of the intestine, making the drug susceptible to degradation or inactivation. Tr. 54:20 to 55:13. To overcome the issue of damage to the enteric coat, the '994 patent teaches an enteric coat made from a combination of enteric-coating agent and sustained-release agent; this combination cushions the granules during tablet compression and prevents cracking of the enteric coat, thereby increasing acid-resistance of the formulation. DTX 2 at col. 2 l. 56 to col. 3, l. 3; col. 9, ll. 9-26; col. 19, ll. 25-31; *see also* Tr. 524:18 to 526:4. The '994 patent discloses an "acid resistance" test (*see* DTX 2, col. 19, ll. 25- 31), which is a "test for the integrity of the granules." Tr. at 526:5-24.

A stated objective of the invention of the '994 patent is good mouth feel, that is, an OTD containing fine granules that do not cause roughness in the mouth. Notably, however, good mouth feel/absence of roughness in the mouth is not a limitation in claim 1 of the '994 patent.

Claim 1 of the '994 patent is as follows:

> 1. An orally disintegrable tablet which comprises (i) fine granules having an average particle diameter of 400 m or less, which fine granules comprise a composition coated by an enteric coating layer comprising a first component

> which is an enteric coating agent and a second component which is a sustained-release agent, said composition having 10 weight % or more of an acid-labile physiologically active substrate that is lansoprazole and (ii) an additive wherein said tablet having a hardness strength of about 1 to about 20 kg, is orally disintegrable.

'994 Patent claim 1, DTX 2; Tr. at 7:24 to 8:7.

B. Person of Ordinary Skill in the Art

The scope and analysis of the '994 patent is to be undertaken by the hypothetical "person of ordinary skill in the art" or "POSA." Defendants' expert, Dr. Meyer-Stout, defined a person of ordinary skill in the art at the time of the filing of the application leading to the '994 Patent as someone with a high level of education (such as a Ph.D. in Pharmaceutical Chemistry or Pharmaceutics), and several years of training or experience devoted to the study of drug formulation and manufacturing, dosage form disintegration, multiparticulate systems and particle size analysis. Tr. at 443:17 to 444:10. Plaintiffs' expert, Dr. Byrn testified that a person of skill in the art at the relevant time would have a lower level of skill, specifically, someone with a college degree in chemistry, pharmaceutical sciences, pharmacy or chemical engineering with at least four years of industry experience. Nevertheless, for the purposes of his testimony at trial, Dr. Byrn assumed that the hypothetical person of skill in the art was the person defined by Dr. Meyer-Stout. As the testimony of Defendants' witness, Dr. Meyer-Stout, and Plaintiffs witness, Dr. Byrn, assumed the same person of skill in the art, the Court need not resolve the dispute between Dr. Byrn's definition and Dr. Meyer-Stout's, and shall accept Dr. Meyer-Stout's definition for the purposes of this analysis.

C. Infringement

1. Burden of Proof and Legal Standards

Plaintiffs have the burden of proving that Defendants infringed the '437 patent by a preponderance of the evidence. *Carroll Touch Inc. v. Electro Mechanical Systems, Inc.*, 15 F.3d 1573, 1578 (Fed. Cir. 1993). It is an act of infringement to submit an application under § 505(j) of the Federal Food, Drug, and Cosmetic Act (*i.e.*, 21 U.S.C. § 355(j)) for a drug claimed in a patent or the use of which is claimed in a patent, if the purpose of such submission is to obtain approval to engage in the commercial manufacture, use, or sale of that same drug before the expiration of such patent. *See* 35 U.S.C. § 271(e)(2)(A); *see also Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1346 (Fed. Cir. 2000) ("[M]ere act of filing an ANDA constitutes infringement."). The question under 35 U.S.C. § 271(e) (2)(A) is whether the drug that is the subject of the ANDA will infringe the patent when approved and marketed. *See Bristol–Myers Squibb Co. v. Royce Labs., Inc.*, 69 F.3d 1130, 1135 (Fed. Cir. 1995). Thus, to meet its preponderance of the evidence burden, the patentee must show that it is more likely than not that the proposed ANDA product would, if commercially marketed, meet the claim limitations of the patent-in-suit. *See Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1287 (Fed. Cir. 2010); *Warner–Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1341 n.15 (Fed. Cir. 2005).

The infringement analysis proceeds in two steps -- the first is proper construction of the relevant claims, and the second is a comparison of those claims to the accused product or method. *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1288 (Fed. Cir. 2009). To prove infringement, the patentee must show that an accused product or method is within the claim limitations of the patent-in-suit either literally or under the doctrine of equivalents. *See*

Amgen, 580 F.3d at 1374; *Warner Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 21, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997). "A patent is infringed if any claim is infringed ... for each claim is a separate statement of the patented invention." *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1220 (Fed. Cir. 1995). Infringement, whether literal or under the doctrine of equivalents, is a question of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

a. Literal Infringement

Literal infringement exists if any one of a patent's asserted claims covers the alleged infringer's product or process. *See Markman v. Westview Instr.*, 517 U.S. 370, 374, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). Literal infringement is shown where each limitation of at least one asserted claim of the patent-in-suit is found in the alleged infringer's product or process. *See Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1562 (Fed. Cir.1990); *Panduit Corp. v. Dennison Mfg. Co., Inc.*, 836 F.2d 1329, 1330 n.1 (Fed. Cir. 1987). Proof of literal infringement may be based on direct or circumstantial evidence. *See Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed.Cir.2009) ("A patentee may prove infringement by any method of analysis that is probative of the fact of infringement ... and circumstantial evidence may be sufficient ....") (citations and internal quotes omitted).

b. Direct Infringement

A person is liable for direct infringement if he "without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefore." 35 U.S.C. § 271(a). Direct infringement requires a party to perform each and every step or element of a claimed method or product." *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir.

2007). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000).

2. Claim Construction

The Court held a *Markman* hearing on May 26, 2011, and subsequently issued its claim construction Opinion. *See* D.I. 113. The Court construed the claim term "fine granules having an average particle diameter of 400 μm or less" to mean "fine granules up to and including the enteric coating layer having an average particle diameter of 400 μm (±10%) or less." D.I. 113 at 7. The evidence at trial showed that a POSA would understand the Court's construction "400 μm (±10%) or less" to mean "440 μm or less." The "+" 10% creates an upper threshold of 440 μm or less (mathematically, 10% of 400 μm is 40 μm; 400 μm plus 40 μm is 440 μm). Tr. at 80:25 to 81:2. A POSA would find the minus 10% immaterial because the minus 10%-- which yields 360 μm or less -- is already encompassed by the 440 μm or less range. Tr. 3/26/13 at 81:3-14 ("because 360 microns is encompassed by the upper threshold of 440 microns, we only pay attention to the 440 micron value"); Tr. 3/28/13 at 480:12-24 ("when you read the patent, you go from 440 and 360 becomes redundant"). Under the Court's construction, the upper limit of the "fine granules" within claim 1 as 440 μm.

In its claim construction Opinion, the Court did not construe the claim term "average particle diameter" finding that there was "no ambiguity with [the] phrase and its ordinary and customary meaning would be clear to one skilled in the art." *See* D.I. 113 at 5.

3. Infringement Analysis

Zydus conceded at trial that its ANDA product would meet all the limitations of claim 1 of the '994 patent but one. D.I. 315 at §2; Tr. at 79:16-21. Zydus disputed that its ANDA

product contains "fine granules having an average particle diameter of 400 µm or less," as that term has been construed by the Court. D.I. 315 at §2; Tr. at 79:16-21. Consequently, a focus of the infringement portion of the trial was the parties' disagreement as to whether individual coated granules in Zydus's ANDA product that are stuck together (referred to as agglomerates) should be deagglomerated into their component, individual coated entities and counted as separate granules for purposes of determining average particle diameter of Zydus's "fine granules." Takeda argued that agglomerates should be deagglomerated into their component, individual parts when determining the average particle diameter of the "fine granules" in claim 1 of the '994 patent. Tr. at 13:25 to 14:6. Zydus, on the other hand, argued that individual granules that become stuck together as agglomerates should be counted as a single particle when determining average particle diameter of the "fine granules" in claim 1 of the '994 patent. Tr. at 15:7-10.

a. A POSA's Understanding of "Fine Granules"

The '994 patent specification and claim 1 of the '994 patent describe "fine granules" as individual, coated granules. DTX 2 at col. 15, l. 26 to col. 16, l. 27, Claim 1. The '994 patent specification describes a "fine granule" as comprising a single "core" that is as uniform a sphere as possible. DTX 2 at col. 15, ll. 33-35; *see also* Tr. at 81:15 to 82:2. This core is coated with a drug layer and then an enteric coating layer to obtain a "fine granule being in the form of a rough sphere." DTX 2 at col. 15, l. 26 to col. 16, l. 27; *see also* Tr. at 81:15 to 82:9. The patent defines "spherical" to include forms with a "curved surface" such as "eggplants and drops." DTX 2 at col. 5, ll. 40-42. But the '994 patent uses "spherical" to describe the shape of the "core," the basic building block of the "fine granule." *See* DTX 2 at

col. 14, l. 40 to col. 15, l. 26. Nowhere does the '994 patent teach that a "fine granule" can be built from more than one spherical core.

Claim 1 is consistent with the teachings of the '994 patent specification. Claim 1 teaches an ODT that includes "fine granules." These "fine granules comprise a composition...having 10 weight % or more of...lansoprazole." DTX 2 at col. 37, ll. 44-51; *see also* Tr. at 82:10-19. That drug composition is, in turn, "coated by an enteric coated layer." *Id.* The "fine granules" of claim 1 refer to individual enteric-coated granules that contain the drug lansoprazole. *Id.*

As Dr. Bugay testified, agglomerates are undesired in the pharmaceutical manufacturing industry; unlike individual coated granules, agglomerates "may not perform in a consistent manner" so that the patient gets "the consistency of the administration of the active [drug] in that tablet." Tr. at 104:4-8, 245:23 to 246:6. Both Plaintiffs' and Defendants' experts agree that the goal of pharmaceutical manufacturing is to generate individual coated granules, not agglomerates. Tr. at 103:13 to 104:3 (Dr. Bugay, Takeda's expert, testifying that the "aim is to produce individual particles, individual granules"); Tr. at 156:18-21; Tr. at 266:16-17 (Dr. Brittain, Defendants' expert, testifying that "ideally what you would like to make are individual particles that receive the coating"). It is the objective of pharmaceutical manufacturing to optimize the process such that one achieves individual coated granules. Tr. at 103:13 to 104:3; 245:20 to 246:16.

Based upon the evidence at trial, the Court concludes that in the context of the '994 patent, a POSA knows to deagglomerate prior to subjecting the sample to particle size measurement; it is the goal of particle size determination to measure individual or primary particles. Tr. at 205:13-21; 105:13-14; 244:15-24. Indeed, the user manual of the HELOS

RODOS – which is the laser diffraction instrument disclosed in the '994 patent as an exemplary particle size measurement instrument (DTX 2 at col. 5, ll. 43-50) – explicitly instructs users that "it needs to be ensured that the sample is free of agglomerates" (emphasis added). *See* PTX 84 at 3.

b. Measuring "Average Particle Diameter"

The '994 patent defines "average particle diameter" to mean "volume based median diameter (median diameter: 50% particle diameter from cumulative distribution), unless otherwise specified." See DTX 2, col. 5, ll. 43-46. The median diameter is commonly known as "d50." Tr. at 92:15-17. The volume based median diameter is referred to as "volume-based d50." Tr. at 92:7-17. Median diameter refers to the value where "50 percent of the particles are above that micron size and 50 percent of the particles are below that micron size." Tr. at 97:24 to 98:2. A POSA would understand that volume-based d50 is a proper measurement of "average particle diameter" in relation to the '994 patent. Tr. at 268:7-21. The parties agree that the "average particle diameter" of claim 1 references "volume based distribution median particle diameter," or d50 for short, as no other measure of average particle diameter is specified. See Tr. at 92:7-17; 267:25 to 269:20.

Although the '994 patent identifies laser diffraction as an example of a method to determine "average particle diameter," that determination is not limited to measurement by that method. *See* DTX 2, col. 5, ll. 46-47 (average particle diameter "can be measured by, for example, a laser diffraction particle distribution measurement method"). As noted earlier, the '994 patent identifies HELOS RODOS as an exemplary laser diffraction instrument. A POSA would understand that other standard measurement methods, such as optical microscopy, can be used to measure average particle diameter. Both parties' experts agree that optical

microscopy is a standard technique for measuring average particle diameter. Tr. at 93:1-2 (Dr. Bugay, Takeda's expert, testifying that optical microscopy is a "standard technique"); Tr. at 338:3-6 (Dr. Brittain, Zydus's expert, agreeing that optical microscopy is a "standard technique").

c. Zydus's ANDA Product

Zydus's ANDA product comes in a 15mg and 30 mg "dosage strength[]." PTX 42 at 1, 13-14; *see also* Tr. at 78:12-15. The product contains fine granules which Zydus refers to in its documents as pellets. PTX 42 at 12; *see also* Tr. at 76:8-17. These pellets "deliver lansoprazole to the patient." Tr. at 76:18-20. Zydus utilizes "the same common pellets" for both 15 mg and 30 mg strengths. PTX 131 at Z0155977 and PTX 132 at Z0156088; *see also* Tr. at 78:22 to 79-10. Thus, the 30 mg strength of the ANDA product is a direct scaleup of the 15 mg strength. Tr. at 78:22 to 79-10.

Zydus's ANDA includes a color-coded depiction that Zydus calls a "[s]chematic representation of enteric coated pellets" for its ANDA product. PTX 42 at 12. This schematic shows that ANDA product's pellets comprise a core coated by the drug layer containing lansoprazole. *See* Tr. at 76:21 to 77:2; see PTX 42 at 12. The drug layer is coated with a barrier coating layer followed by the enteric coating layer. Tr. at 77:3- 14; see PTX 42 at 12. The enteric coating layer protects the lansoprazole in the drug coating layer from the acidic pH of the stomach. Tr. at 77:8-14; *see* PTX 42 at 12. The enteric coating layer is coated by a finishing coating layer. Tr. at 77:15-17; see PTX 42 at 12. The purpose of the finishing coating layer is to "protect[] breakage of the pellets during compression." Tr. at 78:2-11; *see also* PTX 42 at 29.

Both parties' experts describe the granules in Zydus's ANDA product as generally spherical in shape. Dr. Bugay, Takeda's expert, testified that Zydus's pellets are "spheroidal in shape" and "generally spherical." Tr. at 88:7-10; *see also* Tr. at 119:5-6. Dr. Brittain, Zydus's expert, testified that the granules in Zydus's ANDA product are "irregularly-shaped spheres." Tr. at 341:18-20.

The individual coated pellets in Zydus's ANDA product are the "fine granules" of the '994 patent. *See* PTX 42 at 12; *see also* Tr. at 82:20 to 83:14. Dr. Bugay, Takeda's expert, testified that there is a "direct correlation" between Zydus's pellet and the elements of claim 1 of the '994 patent. *Id.*; PTX 42 at 12; PTX 1, Claim 1. In determining the average particle diameter of the "fine granules" of the '994 patent, it is these individual coated pellets that should be subjected to particle size analysis.

[redacted]

d. Agglomerates - Zydus ANDA Product

The vast majority of granules in Zydus's ANDA product are individual granules. A 30 mg Zydus ANDA tablet contains approximately 6,000 individual coated granules. Tr. at 85:19-22; PTX 217. Over 80% of the granules are individual granules. Tr. at 120:20-24; see

also PTX 217. Approximately 18% of the granules are made up of two "fine granules" stuck together, about 1.5% of the granules are made up of three "fine granules" stuck together, and far less than 1% of the granules are three or more "fine granules" stuck together. Tr. at 121:6-12, 121;19-24; *see also* PTX 217.

Dr. Bugay confirmed via Raman spectroscopy that agglomerates in Zydus's ANDA product were comprised of component, individual enteric-coated entities. Tr. at 107:2-7, 108:19 to 110:17; PTX 216; PTX 219. Raman spectroscopy is a "chemical identification technique" that produces an image identifying a compound and where that compound is located in the sample. Tr. at 107:8 to 108:2. Raman spectroscopy showed that, for example, an agglomerate made of two individual pellets in Zydus's ANDA product comprises "two different layers of lansoprazole that are associated with these two granules that are agglomerated together." Tr. at 109:11-19; PTX 216; PTX 219. These "two individual granules [were] adhered together because of the enteric coat." Tr. at 110:8-13; PTX 216; PTX 219. "Zydus's schematic [representation of enteric coated pellets in its ANDA product] corresponds to" the Raman image. Tr. at 110:14-17.

e. Fine Granules in Zydus's ANDA Product

Zydus produced to Takeda 15 mg and 30 mg strength tablets of Zydus's ANDA product. Tr. at 83:16-21; see also PTX 129. The 15 mg strength was from exhibit batch EMM320 and the 30 mg strength was from exhibit batch EMM321. Tr. at 83:22-24; *see also* PTX 129. Both EMM321 and EMM320 were manufactured in March 2012 and completed in June 2012. See PTX 131 at Z0155975; PTX 132 at Z0156086. The EMM320 and EMM321 exhibit batches incorporated pellets from the same exhibit batch EMM227 of "common pellets". PTX 132 at Z0156087 (identifies EMM227 as the batch for the "common pellets"

for the EMM321 batch); PTX 131 at Z0155976 (identifies EMM227 as the batch for the "common pellets" for the EMM320 batch); PTX 133 (batch manufacturing record of the EMM227 "common pellets"). EMM227 was manufactured in March 2012 and completed in May 2012. PTX 133 at Z0155623.

Takeda's expert, Dr. Bugay performed particle size tests on three 30 mg strength tablets of Zydus's ANDA product from the EMM321 batch. Tr. 83:25 to 84:1, 84:25 to 85:1; PTX 130. He tested 100% of the granules contained within each tablet, a total of over 18,000 granules. Tr. 85:2-12, 23-25; PTX 217. According to Dr. Bugay, an "objective of any pharmaceutical manufacturing process is to produce a consistent product from batch-to-batch, tablet-to-tablet." *Id.* His testing was based on a representative sample of Zydus's ANDA tablets. Tr. at 85:2-12, 85:23-25.

Zydus's EMM320 exhibit batch contained 15 mg strength tablets of Zydus's ANDA. The 15 mg strength tablets of Zydus's ANDA product contained the same pellets – *i.e.*, pellets from Zydus's EMM227 exhibit batch – as Zydus's 30 mg strength tablet. See PTX 132 at Z0155976; see also PTX 132 at Z0156087. The 30 mg strength is a direct scale-up of the 15 mg strength. Tr. at 78:22 to 79:10; PTX 131 at Z0155977 and PTX 132 at Z0156088. Because the 30 mg and 15 mg strength tablets use the same common pellets, it was sufficient for Dr. Bugay to test only the 30 mg strength tablets to determine whether the "fine granules" in Zydus's 15 mg and 30 mg ANDA product meet the contested limitation of Claim 1 of the '994 patent. Tr. at 83:25 to 84:6, 117:13-21. There appears to be no dispute that testing of granules from the 30 mg tablet provides comparable results to testing of granules from the 15 mg tablet.

Claim 1 is directed to "fine granules" taken from a compressed tablet. Tr. at 367:12-19 (Zydus's expert testifying that claim 1 is directed to "fine granules within a tablet" and confirming that Dr. Bugay tested the granules within the tablet); 457:18 to 458:5 (Dr. Meyer-Stout opining that the average particle diameter "must refer to the particle size population in the compressed finished tablet" and confirming that Dr. Bugay measured the granules extracted from the compressed finished tablet). To extract the enteric-coated pellets in Zydus's ANDA product, Dr. Bugay used what he described as a "very simple extraction procedure" using an "aqueous buffer solution of pH 4.5." Tr. at 86:22 to 87:15. A washing solution with a pH of 4.5 was selected because the enteric coating layer of Zydus's pellets dissolve at a pH of 5.5 and above. Tr. at 87:16-22. Dr. Bugay chose a washing solution with a pH that was well below the pH required to solubilize the enteric coating layer of Zydus's ANDA pellets. *See id.* That extraction procedure is well known to a POSA. Tr. at 87:23 to 88:1. Dr. Bugay washed each tablet and decanted the filtrate (liquid portion) from the extracted pellets three times. Tr. at 87:3-15.

Dr. Bugay's extraction process freed the pellets from the tablet and removed the finishing coating layer. Tr. at 91:3-16; PTX 42 at 12. That extraction process resulted in enteric-coated pellets that were subjected to particle size analysis. Tr. at 91:3-16; PTX 42 at 12. Dr. Bugay tested the filtrate for the presence of lansoprazole with a high performance liquid chromatography ("HPLC") instrument. Tr. at 88:11-14. Dr. Bugay detected less than 1% lansoprazole in the filtrate for each ANDA tablet that he tested, which demonstrated that Dr. Bugay's extraction process "did not adversely affect the integrity of the enteric coat of the Zydus pellets." Tr. at 88:20-24, 90:20-22; PTX 220. He "did not see any cracking" of the enteric coat. Tr. at 119:11-12. Dr. Bugay used Raman spectroscopy to show that the enteric

coat remained intact after his extraction procedure. Tr. at 110:19 to 111:1, 119:14-21; PTX 214. To the extent that Zydus argues that the extraction procedure could have affected particle size of the "fine granules," the Court finds no evidence of this and notes that Zydus's expert admitted that he did "not perform[] any studies regarding whether extraction of the granules by Dr. Bugay impacted the particle size of Zydus's granules." Tr. at 362:10-17. Additionally, Zydus's own documents reflect that it measured particles extracted from its tablets with no indication of cracking or other degradation. See PTX 70 at 1, 3; Tr. 531:22 - 533:6; Kharkar Dep. Tr. at 116:5-16.

f. Measuring Particles in Zydus's ANDA Product

As noted above, the '994 patent does not limit particle size measurements to any particular method, and the parties' experts agree that optical microscopy is a standard technique to measure average particle diameter. *See* Tr. at 93:1-2; 338:3-6. Both parties' experts acknowledge that laser diffraction and optical microscopy are both "widely recognized," standard techniques that indirectly measure volume- based d50 of irregularly-shaped particles. Tr. at 100:1-9 (testimony of Dr. Bugay, Takeda's expert, stating the similarities of laser diffraction and optical microscopy); Tr. at 338:3-6, 341:15-20, 343:3-14 (testimony of Dr. Brittain, Zydus's expert stating the similarities of laser diffraction and optical microscopy). However, laser diffraction has one limitation that optical microscopy does not have. It is known in the art that laser diffraction "cannot distinguish between...single particles and...clusters of primary particles forming an agglomerate or an aggregate." DTX 64 at 2314, PTX 16 at 1; Tr. at 104:22 to 105:4. "If the presence of aggregates is suspected," the U.S. Pharmacopeia ("USP") – which is a standard setting body – directs POSAs to "other

techniques such as microscopy," when measuring particle size. *See* DTX 64 at 2314, PTX 16 at 1; Tr. at 106:10-17; Trial Tr. 3/28/13 at 486:21-22.

Because "fine granules" in the '994 patent are individual coated entities, if the sample contains more than nominal agglomerates, then optical microscopy is proper; laser diffraction is appropriate if the sample contains individual fine granules with nominal agglomeration. Tr. at 105:25 to 106:9. Consequently, due to laser diffraction's known limitation, laser diffraction is inadequate to measure the volume-based d50 of the "fine granules" in Zydus's ANDA product because about 20% of the granules in Zydus's ANDA product are agglomerates. Tr. at 121:6-12, 121:19-24; PTX 217.

To determine the average particle diameter of the "fine granules" in Zydus's ANDA product, Takeda's expert Dr. Bugay measured volume-based d50 consistent with the teachings of the '994 patent. Tr. 92:18-22; *see also* PTX 1 at col. 5, ll. 43-46. Dr. Bugay used optical microscopy to determine the volume-based d50 of the "fine granules" in Zydus's ANDA product. To obtain the volume-based d50 of the "fine granules" in Zydus's ANDA product, Dr. Bugay used the standard deagglomeration feature included in the image analysis software accompanying his CILAS optical microscope. *See* PTX 19 at 17; Tr. at 111:14 to 113:12.

For the three samples, Dr. Bugay obtained a volume-based d50 of 413.76 μm, 426.94 μm, and 416.24 μm. Tr. at 114:9-13; PTX 217; PTX 218. He averaged these volume-based d50s to determine an average particle diameter of 418.98 μm for the "fine granules" in Zydus's ANDA product. Tr. at 114:3-8; PTX 217; PTX 218. However, due to the presence of less than 1% lansoprazole in the filtrate, Dr. Bugay adjusted the volume-based d50 upward to 420.46 μm. Tr. at 115:24 to 116:19; PTX 217; PTX 218. Thus, the highest possible

volume-based d50 of the "fine granules" in Zydus's ANDA product is 420.46 µm and is still below the upper limit of claim 1 of the '94 patent – 440 µm. Tr. at 117:6-11, 117:22 to 118:4, 137:25 to 138:5. Consequently, Zydus's ANDA product infringes claim 1 of the '994 patent.

[redacted] The Court disagrees.

[redacted] *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241 (Fed. Cir. 2000) ("*Elan*") [redacted] Tr. at 26:14-25. *Elan* involved a patent of Bayer's claiming a drug containing nifedipine crystals of a specific surface area ("SSA") – 1.0 to 4.0 m2/g. *Elan*, 212 F.3d at 1246. Elan amended its ANDA to specify that its drug product would only contain nifedipine crystals with a SSA of 5 m2/g or greater. Along with its ANDA, Elan filed a certificate of analysis ("COA") performed by an independent laboratory, which stated the measured SSA of the nifedipine crystals used in Elan's drug product was 6.15 m2/g. Further, Elan's nifedipine supplier was prohibited from selling in the United States nifedipine with a SSA under 4.7 m2/g. Also, at FDA's request, Elan defined its method of testing to ensure the nifedipine's SSA [size] to be 5 m2/g or greater: Elan would measure the SSA of its nifedipine no more than five business days before tablet manufacture and would discard any nifedipine having a SSA of less than 5 m5/g.

CONFIDENTIAL MATERIAL REDACTED

In *Elan*, the plaintiff Bayer did not contend, nor did it offer any evidence, that Elan's drug would literally infringe its patent. Instead, Bayer speculated that the SSA of the nifedipine crystals would reduce over time to a measurement that fell within the claimed SSA size. Finding Bayer's speculation did not raise an issue of fact, the court granted Elan's motion for summary judgment. *Elan*, 212 F.3d at 1254. The Federal Circuit affirmed, agreeing that Elan's ANDA specification "defines its product in a way that directly addresses the question of infringement – the SSA [size] of nifedipine crystals." *Id.* at 1249-50.

[redacted] Plaintiffs point to *Bayer AG v. Biovail Corp*, 279 F.3d 1340 (Fed. Cir. 2002) ("*Biovail*"), a subsequent case filed by the same plaintiff on the same patent. Based on the first case, Elan argued that Bayer was collaterally estopped from litigating infringement. *Elan* had involved an ANDA for a 30 mg drug product. *Biovail* concerned the same patent at issue in *Elan* and a "nearly identical" ANDA for a 60 mg version of the same drug product. The Federal Circuit held that the "nearly identical" ANDA in the second action did not directly resolve the issue of infringement, and ordered the district court to consider evidence outside the ANDA. *See Bayer AG v. Biovail Corp.*, 279 F.3d 1340, 1346-47 (Fed. Cir. 2002). The factual evidence differed in the Biovail because the plaintiff had done actual testing of Elan's ANDA product. Consequently, evidence derived from the testing of Elan's commercial product created a genuine dispute as to whether Elan's ANDA defined the compound with sufficient particularity to answer the infringement inquiry. *Id.* at 1346-47.

In the instant case, the Court finds, contrary to Defendants' contentions, *Elan* to be inapplicable in light of the testing performed by Plaintiffs' expert on product Zydus intends to commercialize. This testing has shown that the EMM batch contains fine granules with an

average particle diameter less than 440 microns and, therefore, infringes claim 1 of the '994 patent.

[redacted] Tr. at 132:13-23. [redacted] Tr. at 131:5-8. [redacted] PTX 21 at Z0155906; PTX 22 at Z0155924; PTX 23 at Z0155948-49. As stated earlier, laser diffraction does not differentiate between individual granules and agglomerates. Tr. 129:12-20; 302:15 to 303:2, 314:2-13; DTX 64 at 2314; PTX 16 at 1. Defendants' counsel at trial conceded that if the Court were to determine that the '994 patent requires deagglomeration to measure particle size properly (and the Court has so found), [redacted] and Elan would not be not applicable. Tr. 622:17 to 623:24.

[redacted]

Tr. at 132:13-23; 336:6-13 (Zydus uses static sampling). Zydus relies on static sampling to collect enteric coated granules prior to subjecting those granules to particle size testing. Tr. at 335:10 to 336:13. However, Zydus's expert, Dr. Brittain, admits that static sampling does not obtain a representative sample; only dynamic sampling can yield the desired representative sample. Tr. 360:12-24 (agreeing that "only sampling from a bulk powder while it is in motion can yield the desired representative sample").

Given the above, this case is more akin to the circumstances in *Biovail*. Here, Takeda has done actual testing and has evidence that the ANDA product that Zydus intends to commercialize does infringe the Takeda patent such that there is a "genuine disput[e] as to whether the ANDA specification defines the compound with sufficient particularity to answer the infringement inquiry." *See Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). [redacted]. PTX 26 at Zydus-Supp000001; Gurram Dep. Tr. at 56:15-17; 56:19-20. However, when Plaintiffs' expert tested the "fine granules" in the EMM batch, the average particle diameter of those "fine granules" in the EMM batch was less than 440 μm and thus, infringe claim 1 of the '994 patent.

In sum, the Court finds [redacted] that Zydus's ANDA product infringes the '994 patent.

D. Invalidity

1. Burden of Proof

Every claim of an issued patent is independently presumed valid. *See* 35 U.S.C. § 282. Consequently, a party challenging the validity of a patent claim must prove invalidity by clear and convincing evidence, and although the burden of production may switch to the patentee, the burden of proof always remains with the challenger. *See id.*; *Microsoft Corp. v. i4i Ltd. Partnership*, --U.S. --, 131 S.Ct. 2238, 2243, 180 L.Ed.2d 131 (2011); *Innovative Scuba Concepts, Inc. v. Feder Indus., Inc.*, 26 F.3d 1112, 1115 (Fed. Cir. 1994). Clear and convincing evidence is a higher burden of proof than preponderance of the evidence. *See Colorado v. New Mexico*, 467 U.S. 310, 316, 104 S.Ct. 2433, 81 L.Ed.2d 247 (1984). It is

evidence that places in the mind of the finder of fact an abiding conviction that the truth of the factual contentions is highly probable. *See id.* Clear and convincing evidence should "instantly tilt[ ] the evidentiary scales" in favor of its proponent when weighed against the opposing evidence.

2. Written Description and Enablement

One of the statutory conditions for patentability under the Patent Act is adequate disclosure of the invention. As set forth in Section 112 of Title 35,

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112. The Federal Circuit has interpreted § 112 as imposing a number of separate disclosure requirements, two of which are relevant here. The first is known as the written description requirement, found in the first sentence of Section 112, which requires that the specification contain an adequate "written description of the invention." 35 U.S.C. § 112; *see also Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353-54 (Fed. Cir. 2010) (en banc) ("[A] separate requirement to describe one's invention is basic to patent law. Every patent must describe an invention. It is part of the *quid pro quo* of a patent; one describes an invention, and, if the law's other requirements are met, one obtains a patent. The specification must then, of course, describe how to make and use the invention (*i.e.*, enable it), but that is a different task.").

"[T]he purpose of the written description requirement is to 'ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.'" *Ariad Pharms., Inc. v.*

Eli Lilly & Co., 598 F.3d 1336, 1353-54 (Fed.Cir.2010) (en banc). It "serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based and to demonstrate that the patentee was in possession of the invention that is claimed." *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005).

As stated by the Federal Circuit, "[t]he test for sufficiency of a written description is whether the disclosure clearly allow[s] persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Crown Packaging Technology, Inc. v. Ball Metal Beverage Container Corp.*, 635 F.3d 1373, 1380 (Fed. Cir. 2011) (internal quotations omitted, alterations in original). The "hallmark of written description is disclosure," and a court examining the sufficiency of a written description must make "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Ariad*, 598 F.3d at 1351. To pass muster under that inquiry, "[t]he disclosure must reasonably convey[ ] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Crown*, 635 F.3d at 1380 (internal quotations omitted, alteration in original). Said another way, "the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Ariad*, 598 F.3d at 1351.

"[D]etermining whether a patent complies with the written description requirement will necessarily vary depending on the context." *Id.* The requirement "must be applied in the context of the particular invention and the state of the knowledge." *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005). The inquiry into the written description requirement is a question of fact." *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1361 (Fed. Cir. 2011) (quoting *PowerOasis, Inc. v. T–Mobile USA, Inc.*, 522 F.3d 1299, 1307 (Fed. Cir.

2008)). A party challenging a patent based upon the written description requirement must provide clear and convincing evidence that persons skilled in the art would not recognize in the disclosure a description of the claimed invention. *Centocor Ortho Biotech, Inc. v. Abbott Laboratories*, 636 F.3d 1341, 1347 (Fed. Cir. 2011) (presumption of validity overcome only by clear and convincing evidence).

Separate from the written description requirement is the "enablement" requirement codified in § 112. "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *ALZA Corp. v. Andrx Pharmaceuticals, LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010) (quoting *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). "Enablement is not precluded where a 'reasonable' amount of routine experimentation is required to practice a claimed invention, however, such experimentation must not be 'undue.'" *Id.* In *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988), the Federal Circuit set forth the following factors that a court may consider when determining if a disclosure requires undue experimentation:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

858 F.2d at 737. A court need not consider all of the *Wands* factors in its analysis, but rather, a court is only required to consider those factors relevant to the facts of the case. *See Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

Importantly, to fulfill the enablement requirement, the full scope of each claim must be enabled. *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008).

> Enabling the full scope of each claim is part of the *quid pro quo* of the patent bargain. A patentee who chooses broad claim language must make sure the broad claims are fully enabled. The scope of the claims must be less than or equal to the scope of the enablement to ensure that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims.

Id. It is not sufficient for the specification to provide merely "a starting point, a direction for further research"; it must provide "reasonable detail" sufficient to enable a person of ordinary skill in the art to make or use the invention. *Automotive Technologies Intern., Inc. v. BMW of North America, Inc.*, 501 F.3d 1274, 1284 (Fed. Cir. 2007). Whether the enablement requirement has been satisfied is a question of law based upon underlying facts, and is determined as of the patent's effective filing date. *Sitrick*, 516 F.3d at 999.

a. Particle Size Measurement

As noted above, the '994 patent is not limited to particle size measurements conducted by laser diffraction. PTX 1, at col.5, ll. 46-47. The '994 patent specification identifies laser diffraction as an example of a particle size measurement method: "[Average particle diameter] can be measured by, for example, a laser diffraction particle distribution measurement method." *Id.* The Court has recognized that its claim construction of the term "fine granules having an average particle diameter of 400 μm or less" was not limited to particle size measurements by laser diffraction. *See* D.I. 317 at 5 ("Defendants now assert that the Court's claim constructions that incorporate the ±10% deviation apply only to laser diffraction . . . . However, the Court did not construe the above mentioned terms to include any such limitations."). Zydus' expert, Dr. Meyer-Stout, testified that a POSA could turn to methods apart from laser diffraction to measure average particle diameter. See Trial Tr. 3/28/13 at 434:3-11 ("Q. In addition to laser diffraction . . . what methodologies might be available to the

ordinary artisan to determine average particle diameter for granular distribution in the 300 micron to 450 micron size? A. Well, I would consider several methods. Possibly you could use analytical sieving, microscopy, you could use light obscuration methods and you would consider Coulter counter methods.").

Defendants contend that claim 1 of the '994 patent is invalid under 35 U.S.C. §112 for lack of enablement because they allege that there are certain methodologies for the determination of average particle diameter which cannot be utilized without undue experimentation. Specifically, Defendants contend that a POSA would not know what Coulter counter instrument parameters and sample preparation techniques to apply when measuring the particle size of fine granules. Tr. at 631:14 to 632:2. Dr. Meyer-Stout asserted that the average particle diameter of fine granules using a Coulter counter instrument would require "a lot of experimentation" because one would need to consider choosing an adequate electrolyte solution and an adequate aperture tube opening. Tr. at 448:5 to 449:11. Zydus, however, did not offer any more specific evidence of the amount of experimentation necessary to use a Coulter counter instrument or of past failed efforts to use a Coulter counter instrument to measure the average particle diameter of fine granules in an ODT of the '994 patent.

Dr. Byrn testified that "it's well within the person's skill of the art to carry out these measurements and also, the instrument companies are trying to make it turn key. They want to be able to sell their instruments so they want an instrument that's accurate but simple to use . . . . Certainly with a person as high a level as Dr. Meyer-Stout said a Ph.D. with a lot of experience, they would know how to carry out [particle size testing]." Tr. at 514:12-25. The parties do not dispute that a POSA would know how to measure particle size via laser

diffraction and/or optical microscopy. There was no evidence that a POSA would not know what laser diffraction or optical microscopy instrument parameters and sample preparation techniques to apply when measuring the particle size of fine granules. Indeed, Zydus documents showed that Zydus read the '994 patent and measured particle size using laser diffraction without undue experimentation. *See* PTX 70 at 3 ("Particle Size Distribution by Malvern," a laser diffraction instrument); PTX 81 at Z0150600 ("Method specified in patent is Laser diffraction and same method has been used for particle size"); PTX 82 at Z0152877 ("Method specified in patent is Laser diffraction and same method has been used for particle size, mahesh to confirm final particle size analysis method and its parameters"); Tr. at 515:16 to 516:12.

The Court finds that Defendants have failed to establish by clear and convincing evidence that the '994 patent is invalid for lack of enablement based on their allegation that there are certain methodologies for the determination of average particle diameter which could not be utilized without undue experimentation. Defendants rely primarily upon conclusory statements by it expert regarding the amount of experimentation necessary to practice the claim, and such conclusory statements do not carry Defendants' burden. *See Pharm. Res., Inc. v. Roxane Labs. Inc.*, 253 Fed. Appx. 26, 30 (Fed. Cir. 2007).

Zydus also contends that claim 1 of the '994 patent is invalid under 35 U.S.C. §112 for lack of enablement because different particle size measurement methodologies produce different particle size results in relation to the same sample. Tr. at 40:19 to 41:2; 445:1-11. However, Zydus' theory is based on the incorrect assumption that there is only one "correct" average particle diameter for any given unknown sample that can only be measured by one particle size measurement technique. Dr. Byrn testified that a POSA would know that there is

no "single correct particle size" and that "[e]ach method is correct." Tr. at 483:17-23. Dr. Byrn concluded that a POSA would not need to engage in undue experimentation to measure the average particle diameter of fine granules. Tr. at 510:2-8 ("It's clear how to do it and it's within the skill of the art to be able to measure particle size."). Zydus's expert, Dr. Brittain, agreed with Takeda that different particle size results produced by different measurement methods are all equally correct. Tr. at 345:12-25. Dr. Brittain acknowledged that he has published a number of articles that state "the correct but differing particle size results obtained using various instruments are all equally correct, but each simply may be expressing its correct results in different terms." See Trial Tr. 3/27/13 at 345:12 to 346:17 (emphasis added). The Court, therefore, finds that Defendants have failed to show by clear and convincing evidence that claim 1 of the '994 patent is invalid because different particle size measurement methodologies produce different particle size results in relation to the same sample.

b. Inoperative Species

Zydus contends that the Court's claim construction of "fine granules having an average particle diameter of 400 μm or less" as incorporating a ±10% deviation renders the '994 patent invalid under 35 U.S.C. §101 and §112 for lack of enablement because it captures inoperative species – particles greater than a maximum particle size and large, conventional particles. Tr. at 40:14-18.

(i). Maximum Particle Size

The '994 patent defines the term "average particle diameter" as "volume based distribution median diameter (median diameter: 50% particle diameter from cumulative distribution), unless otherwise specified." See PTX 1 at col. 5, ll. 43-46. The '994 patent also refers to a "maximum particle size" that is "practically 425 μm or less." PTX 1 at col. 5, ll.

66-67; Tr. at 282:5 to 283:6 (Dr. Brittain testifying that the '994 patent defines "the maximum particle size" as "practically 425 microns or less"). Dr. Brittain testified that the Court's claim construction "creates trouble" because the average particle diameter limitation encompasses granules greater than 425 μm and that it is a mathematical impossibility for a median to be greater than a maximum. Tr. at 326:2 to 327:8.

However, Zydus's theory incorrectly collapses together two distinct concepts: median/average particle diameter and maximum particle diameter. The '994 patent treats the maximum particle size and the median particle diameter as two separate and distinct concepts. *See* PTX 1 at col. 5, l. 57 to col. 6, l. 3. The '994 patent first describes the median particle diameter in one paragraph and then explicitly sets that concept "aside" by stating "aside from the average particle diameter of the above 'fine granules.'" PTX 1 at col. 5, l. 57-64. The '994 patent then moves on to describe the maximum particle size in the next paragraph:

> In the present invention, "fine granules having an average particle diameter of 400 um or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance" have an average particle diameter of about 400 μm or less, in order that roughness is not felt in the mouth. Preferably, the average particle diameter of the fine granules is 300 to 400 μm.
>
> Aside from the average particle diameter of the above "fine granules", regarding the maximum particle size, the particle diameter is practically 425 μm or less, and preferably practically 400 μm or less. Preferably, the particle diameter is practically 300 to 425 μm, more preferably 300 to 400 μm.

PTX 1 at col. 5, line 57 to col. 6, line 3.

Dr. Byrn testified that claim 1 does not include a maximum particle size limitation but that claim 7 of the '994 patent is directed to maximum particle size. Tr. at 504:5-18; PTX 1 at Claim 1, 7. Claim 7 of the '994 patent claims "[a]n orally disintegrable tablet of claim 1, wherein the particle diameter of the fine granules is practically 425 um or less," which mirrors

the specification's definition of maximum particle size. PTX 1 at claim 7; col. 5, ll. 66-67. Dr. Byrn then testified that he, a POSA, would consider claim 1 to be directed to fine granules with a median diameter of up to 440 μm, while claim 7 is a narrower subset of claim 1, only covering particles that are 425 μm or less. Tr. at 92:7-14 (Dr. Bugay testifying that average particle diameter means median diameter); Tr. at 504:19-24; PTX 1 at Claim 1, 7. If claim 1 were interpreted to include a maximum particle size limitation, claim 7 would be rendered superfluous. *See* PTX 1 at Claim 1, 7. Testimony from Zydus' expert Dr. Brittain supports this conclusion, as he testified that the '994 patent treats the median particle diameter and maximum particle diameter as "two separate and distinct definitions." See Tr. at 282:16-20, 283:9-14.

(ii). Conventional Granules

The '994 patent states, "[c]onventional granules have large particle diameters . . . . Granules having a large particle diameter (400 μm or more of average particle diameter) also produce a feeling of roughness in the mouth." PTX 1 at col. 2, ll. 12-18. Zydus contends that the Court's claim construction would read upon inoperative, conventional granules associated with a bad mouth feel. Tr. at 40:14-18. Dr. Brittain testified that the "Background Art" section of the '994 patent defined conventional granules as having a hard cut off of 400 μm or more. Tr. at 286:25 to 288:5. However, the '994 patent distinguishes the "fine granules" and "conventional granules" concepts. *Compare* PTX 1 at col. 2, ll. 12-18 (stating conventional granules produce a feeling of roughness in the mouth) with PTX 1 at col. 5, ll. 57-63 (stating that fine granules do not produce a feeling of roughness in the mouth). The '994 patent describes "fine granules" as having "an average particle diameter of about 400 μm or less in order that roughness is not felt in the mouth." *See* PTX 1 at col. 5, ll. 57-63. Consistent with

the Court's claim construction, Dr. Byrn testified that a POSA would understand the language "about 400 μm or less " to incorporate a 10% variation and that the patent associates granules of 440 μm or less with a good feeling in the mouth. Tr. at 506:7-25. Thus, a POSA would understand that conventional granules, defined as producing a rough feeling in the mouth, to be 440 μm or greater. Tr. at 507:6-23.

As the Federal Circuit has noted, "[e]ven if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude . . . possible inoperative substances . . . .'" *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984) (citation omitted); *Warner Lambert Co. v. Teva Pharms. USA, Inc.*, Civ. No. 99-922 (DRD), 2007 WL 4233015, at *14 (D.N.J. Nov. 29, 2007). "Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." *Atlas*, 750 F.2d at 1576- 1577; *Pharm. Res.*, 253 Fed. App'x at 30; *see also Warner*, 2007 WL 4233015 at *14 (finding "no evidence in this case that the number of inoperative combinations is so significant as to force one of ordinary skill in the art to experiment unduly in order to practice the claimed invention."). Here, the Court finds that Zydus has not met its burden of proving, by clear and convincing evidence, that claim 1 of the '994 patent is invalid for lack of enablement for capturing inoperative species -- large, conventional particles and particles greater than a maximum particle size.

c. Granules Post-Tableting

Zydus contends that claim 1 of the '994 patent is invalid under 35 U.S.C. § 112 for lack of written description and lack of enablement (a) because the '994 patent does not teach

how to extract granules from a finished tablet for particle size measurement and (b) because the average particle diameter of the granules pre-tableting and post-tableting may not be the same due to the compression forces during tableting. Tr. at 41:3-8; 453:18-22, 455:3-5, 453:23 to 454:13.

(i). Extraction

Dr. Meyer-Stout testified that the '994 patent specification only discloses measurement of pre-tableted granules and does not teach measurement of post-tableted granules (*i.e.*, how to extract granules from a finished tablet for particle size measurement). Tr. at 453:18-22, 455:3-5. It is undisputed that claim 1 of the '994 patent is directed to post-tableted granules. *See* Tr. at 367:12-15; 457:23 to 458:2. Dr. Meyer-Stout and Dr. Brittain both testified that the average particle diameter limitation of claim 1 refers to fine granules within a compressed, finished tablet." Tr. at 367:12-15 ("[Q.] Now, it's your position, isn't it, that the claims of the '994 patent are directed to the fine granules within a tablet. Is that correct? A. Yes, I believe that's exactly what the claim says."); Tr. at 457:18 to 458:2 (Dr. Meyer-Stout agreeing that her expert report states, "The average particle diameter limitation of the claims must refer to the particle size population in the compressed finished tablet"). Defendants offered no evidence that a POSA would not know how to extract granules from a finished tablet prior to subjecting those granules to particle size testing. Defendants also offered no evidence as to how much experimentation would be necessary for a POSA to extract granules from a finished tablet.

According to Takeda's expert, Dr. Byrn, no special training or education is required of a POSA to extract fine granules from a compressed tablet for particle size testing. Tr. at 530:24 to 531:3 ("a technician could do the extraction quite easily"). Indeed, the entire point of an ODT is to allow for easy extraction of granules in a person's mouth. Tr. at 531:12-16

("if it didn't do that, it wouldn't work like an ODT. . . when a person takes an ODT, they're really doing an extraction themselves"). Dr. Bugay measured granules that were extracted from a compressed, finished tablet prior to conducting his particle size analysis. Tr. at 367:17-19; 458:3-5.

It appears based on Zydus's own testing of the particle size of granules during development of its ANDA product that Zydus had no difficulty extracting granules from finished tablets to measure for particle size; there is no evidence of undue experimentation by Zydus. *See* PTX 70 at 1, 3. In an internal e-mail dated March 31, 2009, Zydus indicated that it measured the particle size of "pellets separated from pilot batch tablets," "pellets separated from exhibit batch tablets," and "pellets separated from scaleup batch tablets." *See* PTX 70 at 1, 3; Tr. at 531:22-533:2. Zydus' Rule 30(b)(6) witness, Srinivas Gurram, also confirmed this fact. *See* Gurram Dep. Tr. 127:7-12, 128:4-8 ("[Q.] Is it fair to say that Zydus performed particle size testing on pellets that were extracted from its lansoprazole ODT tablets by Malvern laser diffraction and microscopy? A. Yes, that form of testing, yes."). Zydus' employee in its Intellectual Property Department, Pallavi Kharkar, further testified that Zydus employees were able to measure particle size of granules after they were removed from Zydus' proposed ANDA product. *See* Kharkar Dep. Tr. at 116:5-16 ("Q. So they were able to figure out a way to measure particle sizes after tablet compression? A. I think so.").

Dr. Byrn testified that he did not see any indication in any Zydus documents that Zydus had difficulty extracting granules from tablets prior to subjecting those granules to particle size determination. *See* Trial Tr. 3/28/13 at 533:3-6.

(ii). Compression

Dr. Meyer-Stout also contended the '994 patent is invalid under 35 U.S.C. §112 for lack of written description and lack of enablement because the average particle diameter of the granules pre-tableting and post-tableting may not be the same due to the compression forces during tableting. Tr. at 453:23 to 454:13. Claim 1 of the '994 patent is directed to an ODT with a hardness range of "about 1 to about 20 kg." *See* PTX 1, at Claim 1. Dr. Meyer-Stout asserted that the claimed hardness range corresponds to the amount of compression forces used during tableting; she testified that, the harder the tablet, the more impact compression forces would have on granules in the tablet. Tr. at 451:7 to 452:6 ("as I go to a harder tablet, that those forces would have even more of an impact on the granules in the tablet"). However, Zydus offered no test results evidencing that compression forces would impact particle size. Dr. Meyer-Stout admitted that she did not perform any testing assessing the impact of compression on the particle size of the granules in Zydus' ANDA product. Tr. at 456:21-24 ("I did not perform any tests, yes."). In fact, Dr. Meyer-Stout testified that she could not predict the impact compression forces allowed under the '994 patent would have on the granules:

> Q. What effect would an increase or decrease in hardness strength have on the D(0.50) post-tabletting versus pre-tabletting?
>
> A. Well, if what you're asking, well, post-tabletting, I couldn't predict, for example, the change in the D(0.50) relative to the D(0.50) pre-tabletting. That's just because of all that's going on in the physics of compression. We do fracture some particles, but then they may also fuse to other particles, so I couldn't predict the direction that would go, but in general, one would anticipate in these ranges that as you go up to these higher hardnesses, you would anticipate you may get then an increase in your D(0.50).
>
> Q. Could you also get a decrease in your D(0.50)?

A. That's possible.

Tr. at 454:14 to 455:2.

Zydus also offered no evidence as to how much experimentation is required for a POSA to determine the impact of compression on particle size. In contrast, Dr. Byrn and Dr. Bugay testified that compression forces would not impact the average particle diameter of the fine granules in Zydus' ANDA product. Tr. at 524:1-13; *see also* 118:23 to 119:2 ("[Q.] [L]et's talk about factors that could have impacted your determination of average particle size. What impact did compression forces during tabletting have? A. In my opinion, none."). In fact, Zydus ANDA product contains a finishing coat; the purpose of the finishing coating layer is to "protect breakage of the pellets during compression." *See* PTX 42 at 29; Tr. at 78:2-11. Dr. Bugay also examined the granules first-hand to confirm that the enteric-coated granules were still spherical in shape and thus, compression did not significantly deform the granules. Tr. at 119:3-10.

Dr. Byrn noted that the '994 patent specifically teaches "an orally disintegrable preparation . . . having suitable strength (hardness) so that it will not be damaged through production processes or handling." *See* PTX 1, at col. 2, line 56 to col. 3, line 3; Tr. at 524:18 to 525:6. The '994 patent teaches the inclusion of an enteric coat and sustained release agent in order to cushion the granules during tablet compression and prevent cracking of the enteric coat. PTX 1, at col. 9, lines 9-26; Tr. at 525:19 to 526:4. The '994 patent also discloses an acid resistance test, that is aimed at testing whether the integrity of the enteric-coated granules is damaged during compression. *See* PTX 1, at col. 19, lines 25-31; Tr. at 526:5-22.

Dr. Byrn further testified that compression forces during tableting of an ODT are not so high as to affect the average particle diameter of the granules in an ODT. Tr. at 524:1-13

("We have to remember, ODTs need to dissolve in the mouth. You're giving them to children and people that can't chew very well and so they have to break apart in the mouth. So you can't put [ODTs] under high compression forces that might affect the granules. It's just not common sense."). Dr. Byrn disagreed with Dr. Meyer-Stout's contention that a 20 kg tablet would be "very, very hard" because "it wouldn't be an ODT if it was very, very hard . . . it wouldn't dissolve in the mouth." Tr. at 451:21-22, 528:24 to 529:4. In any event, Dr. Bugay tested Zydus' ANDA product to have a hardness of 3.2 to 3.4 kp. Tr. at 559:2-7.

(iii). *Eli Lilly*

Zydus relies on *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329, 1344 (Fed. Cir. 2010), in support of its contention that the '994 patent is invalid for lack of written description. In *Eli Lilly*, the patent-at-issue claimed drug particles of a specified particle size range. *See* 619 F.3d at 1344. Teva had altered its particle size manufacturing specification of its bulk drug to a non-infringing size. Nevertheless, Eli Lilly's expert tested the particle size of the drug particles in Teva's finished ANDA tablet and determined that, even though the drug particles were not infringing pre-tableting, the drug particles extracted from the finished tablet fell within the claimed size range. The district court construed Eli Lilly's patent as including both pretableted drug particles and post-tableted drug particles. The district court also noted that the patent did not disclose how to extract drug particles from a tablet, nor did the inventors perform any tests to determine how the granulation or the tableting process could affect particle size. The district court then determined that a POSA would not know how to extract particles from a finished tablet for purposes of particle size measurement "so as to make it unnecessary for the inventors to specify the procedure for doing so." *Eli Lilly & Co. v. Teva Pharms. USA*, Inc., 657 F. Supp. 2d 967, 1027 (S.D. Ind. 2009).

Additionally, the district court found that without measuring the drug particle size extracted from a finished tablet, a POSA would not know whether the drug particles were infringing because a POSA would not know whether the drug particle subjected to granulation or tableting would "increase in particle size, decrease, or stay the same." *See id.* at 1027 n.56. Thus, the district court held that Eli Lilly's patent was invalid for lack of written description. *See id.* at 1028.

The Federal Circuit affirmed the district court, noting the district court's finding that a POSA would not know how to extract the drug particles from a finished tablet for particle size measurement and further noting that Eli Lilly's own expert conceded that "[o]ne reading the [Particle Size Patent] in 1996 would not know whether the particle size was being increased or decreased [or remain the same] in the formulation." *See Eli Lilly*, 619 F.3d at 1344-1345 (citation omitted).

Eli Lilly is inapposite. The district court in *Eli Lilly* concluded that a POSA would not know how to extract the particles from a finished tablet for particle size testing. See Eli Lilly, 657 F. Supp. 2d at 1027. Here, a POSA would know how to extract fine granules from a finished ODT for particle size measurement; both parties' experts agreed that Dr. Bugay did precisely that – he measured the particle size of granules extracted from a finished tablet. Tr. 367:17-19; 458:3-5. Zydus' own documents, Rule 30(b)(6) witness, and Intellectual Property Department employee further admitted that Zydus, itself, has successfully extracted granules from a finished tablet for particle size measurement without difficulty. PTX 70, at 1,3; Tr. 127:7-12; 128:4-8; 116:5-16.

Furthermore, in *Eli Lilly*, the district court only considered the impact of compression forces on particle size in the context where a POSA would not know how to extract drug

particles from a finished tablet. *See Eli Lilly*, 657 F. Supp. 2d at 1027 n.56. In contrast, here, a POSA would know how to extract fine granules from an ODT.

The Court finds that Defendants have not met their burden of proving, by clear and convincing evidence, that claim 1 of the '994 patent is invalid for lack of enablement or written description based on allegations that the specification does not teach how to measure post-tableted granules and because the average particle diameter of the granules pre-tableting and post-tableting may not be the same because of compression forces during tableting.

2. Indefiniteness

To be sufficiently definite, a patent specification must "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2. The boundaries of the claim must be discernible to one skilled in the art based on the language of the claim, the specification, and the prosecution history, as well as that person's knowledge of the relevant field of art. *See Halliburton Energy Servs., Inc. v. M–ILLC*, 514 F.3d 1244, 1249–51 (Fed. Cir. 2008). Claims that are "not amenable to construction" or "insolubly ambiguous" are indefinite. *Datamize LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347 (Fed. Cir. 2005). The Federal Circuit has noted that "because claim construction frequently poses difficult questions over which reasonable minds may disagree, proof of indefiniteness must meet an exacting standard." *Haemonetics Corp. v. Baxter Healthcare Corp.*, 607 F.3d 776, 783 (Fed. Cir. 2010) (quotations omitted). "[A] claim is indefinite only if the 'claim is insolubly ambiguous, and no narrowing construction can properly be adopted.' " *Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1338–39 (Fed. Cir. 2003) (*quoting Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).). However, "[i]f the meaning of the

claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Exxon*, 265 F.3d at 1375.

As noted above, the Court has construed the claim term "fine granules having an average particle diameter of 400 μm or less" as incorporating a ±10% deviation. The Court also previously recognized that the '994 patent is not limited to average particle diameter determined by the laser diffraction technique. Zydus contends that the Court's claim construction renders the '994 patent invalid under 35 U.S.C. §112 for indefiniteness. Tr. at 40:9-13. Dr. Brittain testified that when the ±10% variance applied to the "400 μm or less" term, the upper limit is "somewhere between 440 and 360." Tr. at 327:9 to 328:12.

Takeda countered with expert testimony that made clear that a POSA would understand the claim term "400 μm or less ±10%" to refer to an upper limit of 440 μm or less. Tr. 508:5-23. A POSA recognizes that the "minus 10%" or "360 μm" is immaterial because it is already encompassed by the "plus 10%" or "440 μm" limit. Tr. at 81:3-14 ("because 360 microns is encompassed by the upper threshold of 440 microns, we only pay attention to the 440 micron value"); Tr. at 480:12-24 ("when you read the patent, you go from 440 and 360 becomes redundant"). The Court found both of Takeda's experts credible and gives due weight to their testimony in regard to this issue. As such, the Court finds that Defendants did not meet their burden of showing by clear and convincing evidence that the '994 patent is invalid for indefiniteness in light of the Court's construction of the claim term "fine granules having an average particle diameter of 400 μm or less," which incorporated a ±10% variance.

III. REMEDIES

The Hatch–Waxman Act explicitly authorizes several of types of relief for a prevailing patent-holder. *See* 35 U.S.C. § 271(e)(4). Included among these are orders that establish the effective date of FDA approval of the infringing drug as "a date which is not earlier than the date of the expiration of the patent which has been infringed," *id.* § 271(e)(4)(A), and, when appropriate, injunctive relief "against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug." *Id.* § 271(e)(4)(B). A plaintiff seeking a permanent injunction must demonstrate

> (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction.

eBay Inc. v. MercExchange, LLC, 547 U.S. 388 (2006). The Court finds, based on the evidence presented at trial, that Plaintiffs have demonstrated their entitlement to a permanent injunction. In particular, the Court finds that Takeda would suffer irreparable harm if Zydus is not enjoined from launching its generic version of Prevacid SoluTab until expiration of the '994 patent.

As shown at trial, the foundation of Takeda Japan's business is the research and development of innovative pharmaceutical products and the protection of those innovative products through the use of patents. Tr. at 403:7-12. The U.S. based Takeda entities – TPNA, Takeda LLC, and Takeda America – market, promote and sell the drug products developed by Takeda Japan. Tr. at 403:24 to 404:1. The revenues generated from these sales are then

funneled back to Takeda Japan to fund further research and development activities in relation to pipeline products. Tr. at 403:24 to 404:4.

Takeda's Prevacid family includes Prevacid SoluTab and the Prevacid capsules. Tr. at 405:2 to 405:10. After Prevacid capsules lost exclusivity due to expiration of the compound patent (claiming the drug lansoprazole) and generics cannibalized the vast majority of Prevacid capsules' sales and market share, revenues generated by Prevacid SoluTab became much more important for funding research and development opportunities at Takeda Japan. Tr. at 407:3-24, 408:5-10.

In October 2010, Teva launched its generic version of Prevacid SoluTab, [redacted] Tr. at 408:12-14, 410:6-12. Teva was required to withdraw its generic from the market in April 2011 due to problems with clogging nasogastric tubes and oral syringes. Tr. at 410:13-20. [redacted] Tr. at 410:21-25. Upon the withdrawal of Teva's generic [redacted] Prevacid SoluTab regained its status as the only ODT PPI available in the marketplace. Tr. at 411:7-11.

Presently, Prevacid SoluTab is the only ODT PPI available in the marketplace. Tr. at 411:7-13. As Dr. Fennerty testified, Prevacid SoluTab is especially suited for patient populations who have difficulty swallowing, such as the pediatric population. Tr. 55:14 to 56:4.

Upon entry into the market, Teva's generic immediately and significantly cannibalized the vast majority of sales and market share of Prevacid® SoluTabTM. *See* PTX 127; PTX 224; Tr. at 413:4-13.

Prior to generic entry, [redacted] *See* PTX 127; Tr. at 413:23 to 414:8. According to Mr. Zaeske testified, if no generic ever launched, he would expect Prevacid SoluTab to continue generating [redacted] consistent with its historical performance. Tr. at 417:16-22. Thus, Takeda never fully recovered from the harm caused by generic entry, even though all generics were eventually withdrawn from the market. *See* PTX 127; Tr. at 413:23 to 414:2 ("SoluTab product regained a portion of its sales but does not fully return to its historical monthly gross sales level"), 414:9-13 ("initial generic entry permanently damaged Prevacid® SoluTabTM, the brand, in terms of its revenue potential").

If Zydus were to launch its ANDA product, Takeda would suffer the same, permanent harm that it suffered as a result of Teva's generic – immediate cannibalization of market shares and sales. Tr. at 420:19 to 421:1. Similar to the impact of Teva's generic, Takeda would likely not be able to fully recover from the damage caused by entry of Zydus' generic prior to expiration of the '994 patent. Tr. 3/28/13 at 414:9-13. According to witness testimony, cannibalization of Prevacid SoluTab revenues will ultimately mean less funding for global research and development efforts by Takeda Japan. Tr. at 421:14-23. Plaintiff would be irreparably harmed in that they would lose research and development opportunities that could have been funded by Prevacid SoluTab revenues if Zydus' ANDA product is

allowed to enter the market. Tr. 421:24 to 422:5, 427:5-9 ("the value of those R&D activities is impossible to quantify") (emphasis added).

Plaintiff's evidence of harm went unrebutted, and Zydus did not offer any evidence of harm Zydus would experience if it were enjoined from launching its ANDA product. The Court finds that the relevant factors weigh in favor of enjoining Zydus from engaging in the commercial manufacture, use, offer for sale or sale within the United States, or importation into the United States, of Zydus's ANDA product until expiration of the '994 patent.

IV. CONCLUSION

As set forth above, the Court finds that Zydus infringed claim 1 of the '994 patent. The Court further finds that Defendants have not established by clear and convincing evidence that claim 1 of the '994 patent is invalid. Consequently, judgment shall be entered in favor of Plaintiffs.

/s/ Joel A. Pisano
JOEL A. PISANO, U.S.D.J.

Dated: May 7, 2013

ADDENDUM 3

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL CO, LIMITED, et al. Plaintiff, v. ZYDUS PHARMACEUTICALS USA INC., et al. Defendant.	Civil Action No. 10-1723 (JAP) **OPINION**

PISANO, District Judge.

Plaintiffs Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals North America, Inc., Takeda Pharmaceuticals LLC, Takeda Pharmaceuticals America, Inc., and Ethypharm, S.A. (collectively, "Takeda" or "Plaintiffs") bring this Hatch-Waxman patent infringement action against defendants Zydus Pharmaceuticals (USA) Inc. and Cadila Healthcare Limited (together, "Defendants") claiming infringement of three patents alleged to cover Takeda's Prevacid SoluTab product ("SoluTab"): U.S. Patent Nos. 6,328,994 (the " '994 patent"), 7,431,942 the " '942 patent"), and 5,464,632 (the " '632 patent").

Presently before the Court is the parties' request for claim construction. The Court held a *Markman* hearing on May 26, 2011. This Opinion addresses the proper construction of the disputed claim terms.

I. The Technology and Patents-In-Suit

The three patents at issue claim a pharmaceutical dosage form known as an orally disintegrating tablet ("ODT"). An ODT is a tablet formulation that disintegrates in the mouth rapidly in the presence of saliva without the need for water. An ODT provides advantages to children, the elderly or anyone who may have difficulty swallowing conventional tablets and capsules.

The '994 and '942 patents, both entitled "orally disintegrable tablets", concern ODT formulations containing fine granules of enteric-coated acid-labile drug. The '632 patent, entitled "rapidly disintegrating multiparticular tablet", claims an ODT with excipient mixture of a swelling agent and disintegrating agent that allows it to disintegrate rapidly in the mouth in less than 60 seconds. Upon disintegration, the active substance is present in the form of coated microcrystals or coated or uncoated microgranules.

II. Standards for Claim Construction

In order to prevail in a patent infringement suit, a plaintiff must establish that the patent claim "covers the alleged infringer's product or process." *Markman v. Westview Instrs., Inc.*, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). Consequently, the first step in an infringement analysis involves determining the meaning and the scope of the claims of the patent. *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 988 (Fed. Cir. 1995). Claim construction is a matter of law, *Markman v. Westview Instrs., Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) *aff'd* 517 U.S. 370 (1996), therefore, it is "[t]he duty of the trial judge . . . to determine the meaning of the claims at issue." *Exxon Chem. Patents, Inc. v. Lubrizoil Corp.*, 64 F.3d 1553, 1555 (Fed. Cir. 1995).

In *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), the Federal Circuit emphasized that "[i]t is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." 415 F.3d 1312 (internal quotations omitted) (citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576 (Fed. Cir. 1996) ("we look to the words of the claims themselves . . . to define the scope of the patented invention"); *Markman*, 52 F.3d at 980 ("The written description part of the specification itself does not delimit the right to exclude. That is the function and purpose of claims."). Generally, the words of a claim are given their "ordinary and customary meaning," which is defined as "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Id.* at 1312-13 (citations omitted). In this regard, the Federal Circuit has noted that

> It is the person of ordinary skill in the field of the invention through whose eyes the claims are construed. Such person is deemed to read the words used in the patent documents with an understanding of their meaning in the field, and to have knowledge of any special meaning and usage in the field. The inventor's words that are used to describe the invention--the inventor's lexicography--must be understood and interpreted by the court as they would be understood and interpreted by a person in that field of technology. Thus the court starts the decisionmaking process by reviewing the same resources as would that person, viz., the patent specification and the prosecution history.

Id. (quoting *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1477 (Fed.Cir.1998)).

In the process of determining the meaning of a claim as understood by a person of ordinary skill in the art, a court may look to various sources from which the proper meaning may be discerned. These sources include "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* at 1314.

While a court is permitted to turn to extrinsic evidence, such evidence is generally of less significance and less value in the claim construction process. *Id.* at 1317. Extrinsic evidence would include evidence that is outside the patent and prosecution history, and may include expert testimony, dictionaries and treatises. *Id.* The Federal Circuit has noted that caution must be exercised in the use of extrinsic evidence, as this type of evidence may suffer from inherent flaws affecting its reliability in the claim construction analysis. *Id.* at 1319 ("We have viewed extrinsic evidence in general as less reliable than the patent and its prosecution history in determining how to read claim terms."). While "extrinsic evidence may be useful to the court, . . . it is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence."

III. The Disputed Claim Terms

The parties have identified a number of disputed claim terms in each patent. The Court will address each of these in turn.

1. The '994 Patent

a. *"fine granules having an average particle diameter of 400 µm or less"*

This phrase appears in Claim 1 of the '994 patent. Plaintiffs contend that this phrase means "fine granules up to and including the enteric coating layer having an average particle diameter of 400 µm (±10%) or less." D.I. 94 at Revised Ex. A at 1. Defendants argue that the Court should construe the phrase as meaning the following:

> "fine granules having an average particle diameter of precisely 400 µm or less" wherein the term "average particle diameter" references the "median diameter" value of the fine granules (as set forth in the specification of U.S. Patent No. 6,328,994 col. 5, ll. 43-46, when measured within the tablet (as set forth in claim 1).

Id. at 1. Defendants to not dispute that the coating of the composition is measured when determining average particle diameter.

The parties dispute as to this claim term is two-fold. The first dispute centers on the phrase "average particle diameter" within the disputed claim term. Plaintiffs argue that no construction is necessary and the plain and ordinary meaning of the phrase should apply. Defendants, on the other hand, argue that "average particle diameter" is limited to the "median diameter" value of the fine granules when measured within the tablet. However, the portion of the specification relied upon by the Defendants does not limit "average particle diameter" to just the median diameter. Indeed, the specification states that "[a]verage particle diameter means volume based distribution median diameter (median diameter: 50% particle diameter from cumulative distribution), *unless otherwise specified*." '994 patent, col. 5, lines 43-45 (emphasis added). Thus, to extent that Defendants seek a construction of the phrase "average particle diameter", the Court sees no reason to limit it as Defendants contend. The Court finds no ambiguity with phrase and its ordinary and customary meaning would be clear to one skilled in the art. Therefore, no construction is necessary.

The parties' remaining dispute centers on whether the claim limitation of "400μm or less" should be read as 400μm (± 10%) or as "precisely" 400 μm or less. As Plaintiffs point out, the specification is clear that "fine granules having a particle diameter of 400 μm or less" is not precise. First, the specifications states:

> In the present invention, "fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance" have an average particle diameter of about 400 μm or less, in order that roughness is not felt in the mouth.

'994 patent, col. 5, lines 57-63. It further states elsewhere: "[E]specially when used in an orally disintegrable tablet, the average particle diameter of the included granules must be about 400 μm or less, preferably about 350 μm." *Id.*, col. 2, lines18-21. Thus, the specification correlates "average particle diameter of 400 μm or less" with "an average particle diameter of *about* 400 μm or less."

The specification in the '994 patent notes that a measurement of "average particle diameter" can be obtained utilizing a laser diffraction particle distribution method, for example, "a method using Raser Diffraction Analyzer, type: HEROS RODOS [trade name; manufactured by Sympatec (Germany)]. '994 patent, col. 5, lines 46-47 (brackets in original). This is, in fact, the instrument used in performing such an analysis with respect to the examples in the specification. *See* '994 patent, col. 19, lines 32-37. According to Plaintiff's expert, Dr. Byrn, a deviation of 10% for measurements by laser diffraction particle distribution is universally accepted. *See* Byrn Decl. ¶¶ 28-30. In support of his conclusion, Dr. Byrn points to the U.S. Pharmacopeia ("USP") standard, which has been accepted and used by others skilled in the art. See *id.*, Ex. 6.

Defendants dispute the applicability of 10% deviation figure. Defendants, however, do not necessarily dispute in substance the authorities relied upon by Dr. Byrn, but rather argue that the authorities relied upon by Dr. Byrn postdate the relevant patent application. Based upon an academic publication from 2002, Defendants argue that the figure during the relevant time period was not 10%, but rather was less than 3%. See Def. Brf. at 10 (citing R. Xu, *Paricle Characterization: Light Scattering Methods* (2002) at 166 ("… a modern commercial instrument should easily achieve a relative standard deviation less than 3% of the median value in repeat measurement…"). However, the Court is not persuaded by such

reference, as Defendants provide no basis for the Court to conclude that the state of the technology is such that its accuracy actually became worse over time.

For the reasons above, the Court shall adopt Plaintiff's construction, and define "fine granules having an average particle diameter of 400 μm or less" to mean "fine granules up to and including the enteric coating layer having an average particle diameter of 400 μm (±10%) or less."

b. *"said composition having 10 weight % or more of an acid-labile physiologically active substance that is lansoprazole"*

This phrase appears in Claim 1 of the '994 patent. Plaintiff argue that this disputed phrase should be construed as "said composition up to but not including the enteric coating layer having 10 weight % or more of an acid-labile physiologically active substance that is lansoprazole". D.I. 94 at Revised Ex. A at 2. Defendants, on the other hand, contend that this claim limitation does not require construction and should be considered to have its plain meaning. If, however, the Court determines that construction is appropriate, Defendants argue that this phrase should be construed as: "said composition is an enteric coated granule having 10 weight % or more of an acid-labile physiologically active substance that is lansoprazole". *Id.*

The basic difference in the parties' construction centers on whether the "composition" includes the enteric coating layer (as Defendants contend) or excludes the enteric coating layer (as Plaintiffs contend). The Court finds that the claim language itself dictates the Plaintiffs' construction. Claim 1 of the '994 patent reads as follows:

> An orally disintegrable tablet which comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer comprising a first component

> which is an enteric coating agent and a second component which is a sustained-release agent, said composition having 10 weight % or more of an acid-labile physiologically active substrate that is lansoprazole and (ii) an additive wherein said tablet having a hardness strength of about 1 to about 20 kg, is orally disintegrable.

As the "composition" is "coated by an enteric coating layer", the "composition" must necessarily be exclusive of the enteric coating layer. Further, contrary to the arguments of Defendants, the Court finds in the record no "clear and unmistakable disclaimer" of such a reading by the patentee. *See Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1342 (Fed. Cir. 2009) (disclaimer may be found "only if the allegedly disclaiming statements constitute a clear and unmistakable surrender of subject matter …. Even if an isolated statement appears to disclaim subject matter, the prosecution history as a whole may demonstrate that the patentee committed no clear and unmistakable disclaimer.) (internal quotations and citations omitted).

Consequently, the Court construes "said composition having 10 weight % or more of an acid-labile physiologically active substance that is lansoprazole" consistent with Plaintiff's proposed construction: "said composition up to but not including the enteric coating layer having 10 weight % or more of an acid-labile physiologically active substance that is lansoprazole".

c. *"wherein the average particle diameter of the fine granule is 300 to 400 µm"*

This phrase appears in claim 2 of the '994 patent. Plaintiffs proffer the following proposed construction: "wherein the average particle diameter of the fine granule is 300 to 400 µm (±10%)". D.I. 94 at Revised Ex. A at 4. Defendants argue that the Court should construe the phrase as meaning the following:

> "fine granules having an average particle diameter of precisely 400 µm or less" wherein the term "average particle diameter" references the "median diameter" value of the fine granules (as set forth in the specification of U.S. Patent No. 6,328,994 col. 5, ll. 43-46, when measured within the tablet (as set forth in claim 1).

Id.

For the reasons above in section III(1)(a) of this Opinion (construing "fine granules having an average particle diameter of 400 µm or less"), the Court adopts Plaintiffs' proposed construction, and shall construe "wherein the average particle diameter of the fine granule is 300 to 400 µm" as meaning "wherein the average particle diameter of the fine granule is 300 to 400 µm (±10%)". The phrase "average particle diameter" shall have its plain and ordinary meaning as understood by one skilled in the art.

2. The '942 Patent

a. *"fine granules having an average particle diameter of 300 to 400 µm"*

This phrase appears in claim 1 of the '942 patent. Plaintiffs contend the limitation should be construed as meaning "fine granules up to and including the enteric coating layer and mannitol coating layer outside the enteric coating laying having an average particle diameter of 300 to 400 µm (±10%)". D.I. 94 at Revised Ex. A at 6. Defendants argue that the phrase should be construed as follows:

> "fine granules having an average particle diameter of precisely 300 to 400 µm or less" wherein the term "average particle diameter" references the "median diameter" value of the fine granules (as set forth in the specification at U.S. Patent No. 6,328,994 col. 5, ll. 43-46), when measured within the tablet (as set forth in claim 1)

Id.

Defendants do not dispute that the fine granules comprise a composition coated by an enteric coating layer and a coating layer comprising mannitol outside the enteric coating

layer, and do not dispute that such coatings are measured when determining average particle diameter. Consequently, for the reasons above in section III(1)(a) of this Opinion (construing "fine granules having an average particle diameter of 400 µm or less"), the Court adopts Plaintiff's proposed construction, and shall construe "fine granules having an average particle diameter of 300 to 400 µm" as meaning "fine granules up to and including the enteric coating layer and mannitol coating layer outside the enteric coating laying having an average particle diameter of 300 to 400 µm (±10%)". The phrase "average particle diameter" shall have its plain and ordinary meaning as understood by one skilled in the art.

3. The '632 Patent

a. *"permits to obtain reduced ph influence in the digestive tract"*

This term appears in claim 1 of the '632 patent. Claim 1 reads as follows:

> A rapidly disintegratable tablet for oral administration and disintegration in the buccal cavity without the use of water, wherein said tablet comprises an active substance and a mixture of non-effervescent excipients and permits to obtain reduced pH influence in the digestive tract and reduced influence of viscosity, said active substance being multiparticulate and in the form of coated microcrystals, or coated microgranules and wherein said mixture of excipients comprises a disintegrating agent and swelling agent which are responsible for the disintegration of the tablet with the saliva present in the mouth, to achieve in less than 60 seconds a suspension easy to swallow.

'632 patent, claim 1. Plaintiffs argue that "permits to obtain reduced ph influence in the digestive tract" as it appears in this claim should be construed to mean "the active ingredient in the tablet is less influenced by stomach pH (*i.e.*, the drug is coated)". D.I. 94 at Revised Ex. A at 8. Defendants contend that the claim limitation is indefinite and does not require construction.

"[A] claim is indefinite only if the 'claim is insolubly ambiguous, and no narrowing construction can properly be adopted.' " *Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d

1332, 1338-39 (Fed. Cir. 2003) (quoting *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).). "If the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Exxon*, 265 F.3d at 1375.

The ' 632 patent teaches that one of the invention's features is, among others, "reduced pH influence in the digestive tract":

> the tablet according to the invention has all the advantages of coated particles which permit to obtain especially a taste-masking, a gastroresistance, a delayed release as well as all the advantages of the multiparticulate forms with modified action or non-modified action, i.e. a great exchange surface, the dispersion, less inter- and intra-individual variations, a very reduced gastric emptying influence as well as **reduced pH influence in the digestive tract**, reduced influence of viscosity and consequently of food and of the position of the body, without local toxic manifestation.

'632 patent, col. 3, lines 41-51 (emphasis added). The patent also teaches that one of the advantages of using a coated multiparticulate dosage form is "gastroresistance," or resistance to the acidic environment of the stomach. *See id.; see also id.* at col. 7, lines 9-14 ("it consists of a tablet which combines a high level technology (control release, of gastroresistance, of taste-masking of the active principle) with a high security of use due to its multiparticulate form by way of the coating during the process of manufacture and to the fact that is disintegration occurs in the mouth, …"). However, contrary to the contentions of Plaintiff, nothing in the specification or the testimony of Defendants' expert, who testified that the invention's "formulation design should lead to gastroresistance," definitively correlates gastroresistance to phrase "reduced ph influence in the digestive tract." In fact, the specification would imply otherwise, as "gastroresistance" and "reduced pH influence in the digestive tract" are listed independently in the portion of the specification quoted above.

That being said, the Court is also not persuaded, at least at this juncture, that the term is unable to be construed and, therefore, indefinite. Overall, the parties simply did not adequately justify their respective arguments. For example, in the parties' joint claim construction chart, Plaintiffs cite to the January 5, 2000 Amendment (Ex. 10 to Byrn Decl.) submitted to the PTO in support of their construction of this term. This Amendment, in the relevant part, states as follows:

> By this amendment, claims 1 and 6 have been cancelled, claim one is replaced with new claim 1 … New claim 1 has been drafted in order to meet objections 1 and 2 page 3 of the action by incorporation of positive language. In that respect the language << Free of acids and of any substance which develops high viscosity in contact with water >> is replaced by << permits to obtain reduced pH influence in the digestive tract and reduced influence of viscosity >>.

Byrn Ex. 10 at TAKZ0001270. Nevertheless, although cited by Plaintiffs, neither party addressed the prosecution history as it relates to this disputed term in much more than a conclusory fashion. Consequently, construction of "reduced ph influence in the digestive tract" shall await summary judgment or trial.

b. *"permits to obtain … reduced influence of viscosity"*

This term appears in claim 1 of the '632 patent. Plaintiffs argue that this limitation should be construed to mean "the formulation influences viscosity less than the prior art formulations of record that have excipients increasing viscosity". D.I. 94 at Revised Ex. A at 9. Defendants contend that the claim limitation is indefinite and does not require construction.

The Court finds that the intrinsic evidence, specifically the prosecution history, supports Plaintiffs' proposed construction. During prosecution, the patentee amended Claim 1 of the patent to include this limitation in order to overcome prior-art references, U.S. Patent

4,886,669 and its counterpart EP 273,005 ("the Zyma references"). Byrn Decl. ¶ ¶ 49-50, Exs. 7 and 8. The Zyma references disclose tablets that use excipients to increase viscosity. Here, the patentee included this specific claim language with respect to viscosity in order to distinguish over the prior-art Zyma references:

"The proposed claim differs from the [US Zyma] reference in that it defines tablets which are free of any substance which develops a high viscosity when in contact with water."

"The proposed claim differs from the [EP Zyma] reference in that it defines tablets which are free of any substance which develops a high viscosity when in contact with water."

Byrn Decl. ¶ 51, Ex. 9. The specification uses the phrase "reduced influence of viscosity," '632 patent, col. 3, lines 49-50, so it is logical that the patentee subsequently amended its former viscosity- related claim language to "permits to obtain . . . reduced influence of viscosity." The Court, consequently, shall construe the disputed claim term consistent with Plaintiff's proposed construction.

c. *"said active substance being multiparticulate and in the form of coated microcrystals, or coated microgranules"*

This term appears in claim 1 of the '632 patent. Plaintiffs propose the following construction: "the active substance is multiparticulate, where individual microcrystals or microgranules containing the active ingredient are entirely coated (*i.e.*, not monolithic)". D.I. 94 at Revised Ex. A at 10. Defendants argue that this limitation does not require construction as its meaning is plain. To the extent that the Court may find construction of the phrase necessary, Defendants propose the following construction: "the active substance being multiparticulate and in the form of coated microcrystals, or coated microgranules". *Id.*

The Court discerns no ambiguity in the term and finds that its ordinary and customary meaning would be clear to one skilled in the art. Consequently, the Court agrees with Defendants that no construction of this term is necessary. Rather, the plain meaning of the term as understood by someone of ordinary skill shall apply.

d. *"disintegrating agent"*

This term appears in claim 1 of the '632 patent. *See* claim 1 ("wherein said mixture of excipients comprises a disintegrating agent and swelling agent which are responsible for the disintegration of the tablet with the saliva present in the mouth"). Plaintiffs assert that this claim term means "a substance, or mixture of substances, added to a tablet to facilitate its breakup or disintegration after administration". D.I. 94 at Revised Ex. A at 11. Defendants, on the other hand, propose the following construction: "a substance, which is not a direct compression sugar, sucrose or lactose, that is a causal agent in the breakup or disintegration of the tablet by a function other than dissolution, and which, in accord with its art-recognized definition, breaks the tablet into smaller particles that dissolve more rapidly than in the absence of the disintegrant". *Id.*

The parties first dispute whether a disintegrating agent must be a causal agent in the breakup of the tablet or merely facilitates disintegration. Plaintiff argues that both the disintegration agent and the swelling agent are needed for disintegration and, therefore, the "disintegration agent" merely facilitates, rather than causes, disintegration. Defendants argue that the disintegration agent must be a causal agent in the disintegration of the tablet.

Exactly the same issue and arguments regarding the same patent and claim term were addressed by the court in *Takeda Pharmaceutical Co. Ltd. v. Teva Pharmaceuticals USA, Inc.*, 668 F.Supp.2d 614 (D. Del. 2009):

> The parties do take issue as to whether a disintegrating agent, as contemplated by claim 1, must "cause" disintegration or merely "facilitate" disintegration. The extrinsic references identified by the parties define "disintegrating agent" as a substance that both "facilitates" and "causes" the breakup or disintegration of a tablet. Looking to the specification, the examples identified as disintegrating agents are known in the art as "super-disintegrants," *i.e.*, excipients whose disintegrating characteristics bear a strong causal relationship to the breakup of a tablet. Super-disintegrants are classified as such due to the comparatively low amount of excipient required to achieve the disintegration of a formulation.
>
> Like the specification, the prosecution history is more consistent with a construction requiring an agent that "causes" disintegration. During prosecution, the examiner rejected the claims of the application leading to the '632 patent ("the application") as unpatentable over U.S. Patent No. 5,073,374 granted to McCarty ("McCarty"). McCarty teaches a quickly dissolving tablet comprising a soluble API, a lubricant and "a soluble, directly compressible tablet excipient." The soluble excipient disclosed in McCarty "is typically a sugar, such as sucrose or lactose." Although claim 1 of McCarty describes a buccal tablet where "... disintegration occurs from 0.5 to 5 minutes after administration" (emphasis added), in traversing the rejection, the patentee nevertheless alleged that McCarty "clear[ly] ... does not teach disintegrating agents."

Teva, 668 F.Supp.2d at 621. Judge Robinson concluded that

> [i]n light of the descriptions of "disintegrating agent" given in the specification and the prosecution history, the court concludes that a causal relationship must exist between the disintegrating agent and the act of disintegration. Put another way, excipients that facilitate disintegration, but are not known in the art to cause disintegration as "disintegrating agents," will not fall within this limitation.

Id.

This Court agrees with Judge Robinson's reasoning and conclusion. Based upon intrinsic evidence, a "disintegrating agent" must have a causal effect on the act of disintegration.

The second area of dispute regarding this term involves Defendants' claim that a disintegration agent cannot be a direct compression sugar, sucrose or lactose. Defendants argue that the patentee disavowed these substances in order to distinguish over the McCarty

reference. However, the Court, having reviewed the prosecution history, does not find the "clear and unmistakable disclaimer" that would be required for Defendants' argument to prevail.

Consequently, the Court shall adopt a construction that combines both parties' proposals and construe "disintegrating agent" as "a substance, or mixture of substances, added to a tablet that is a causal agent in its breakup or disintegration after administration."

e. *"swelling agent"*

This term appears in claim 1 of the '632 patent. Plaintiffs offer the following proposed construction: "a substance, or mixture of substances, which, when contacted with liquid, absorbs the liquid and expands in volume". D.I. 94 at Revised Ex. A at 12. Alternatively, Defendants assert that this term should be construed to mean "a non-causal agent in the disintegration or break-up of the table constituting a three-dimensional network of hydrophilic polymer chains that are chemically or physically crossed linked which absorb either aqueous or organic solutions and thereby expand from 10 to 1,000 times their own weight". *Id.*

The Court finds Plaintiffs' proposed construction to be more in accord with the intrinsic evidence and the customary meaning of the term "swelling agent" to persons of ordinary skill in the art. As Plaintiffs point out, the term "swelling agent" was a well-known term of art at the relevant time. *See* Byrn Decl. ¶ 72, Exs. 18-21. The *Teva* court noted that the "ordinary meaning" of swelling agent is "a substance which, when contacted with liquid, absorbs the liquid and expands in volume." *Teva*, 668 F.Supp.2d at 621.[1] Nothing in the specification or claims of the '632 patent indicates that a different definition for swelling

[1] The parties in that case did not dispute this construction.

agent should apply. Consequently, the Court construes "swelling agent" as "a substance, or mixture of substances, which, when contacted with liquid, absorbs the liquid and expands in volume".

f. *"to achieve in less than 60 seconds a suspension easy to swallow"*

This term appears in claim 1 of the '632 patent. Plaintiffs contend that the phrase means "the mean time to achieve a suspension easy to swallow is less than 60 seconds." *Id.* at 13. Defendants argue that the claim limitation does not require construction and should be considered to have its plain meaning. Alternatively, Defendants propose the following construction: "the absolute time to achieve a suspension easy to swallow is precisely less than 60 seconds". *Id.*

The Court discerns no ambiguity in the term and finds that its ordinary and customary meaning would be clear to one skilled in the art. Consequently, the Court agrees with Defendants that no construction of this term is necessary. Rather, the plain meaning of the term as understood by someone of ordinary skill shall apply.

IV. Conclusion

For the reasons set forth above, the disputed claim terms will be construed as indicated. An appropriate Order shall accompany this Opinion.

/s/ Joel A. Pisano
JOEL A. PISANO, U.S.D.J.

Dated: October 5, 2011

ADDENDUM 4

US006328994B1

(12) **United States Patent**
Shimizu et al.

(10) **Patent No.: US 6,328,994 B1**
(45) **Date of Patent: Dec. 11, 2001**

(54) **ORALLY DISINTEGRABLE TABLETS**

(75) Inventors: **Toshihiro Shimizu**, Itami; **Shuji Morimoto**; **Tetsuro Tabata**, both of Suita, all of (JP)

(73) Assignee: **Takeda Chemical Industries, Ltd.**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(51) **Int. Cl.**[7] **A61K 9/14**; A61K 9/20; A61K 9/46; A61K 9/16

(52) **U.S. Cl.** **424/489**; 424/464; 424/465; 424/466; 424/490; 424/493

(58) **Field of Search** 424/464, 465, 424/466, 489, 490, 493

(56) **References Cited**

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WO 96/01624 1/1996 (WO) .
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(57) **ABSTRACT**

An orally disintegrable tablet, of the present invention, which comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive, has superior disintegrability or dissolution in the oral cavity so that it can be used for treatment or prevention of various diseases, as an orally disintegrable tablet capable of being administered to the aged or children and easily administered without water. Also, because the tablet of the present invention contains fine granules having the average particle diameter such that it will not impart roughness in mouth, it can be administered easily without discomfort at the administration.

45 Claims, No Drawings

ORALLY DISINTEGRABLE TABLETS

This application is a 371 of PCT/JP99/02548 filed May 17, 1999.

This application is the National Stage of International Application Serial No. PCT/JP99/02548, filed May 17, 1999.

TECHNICAL FIELD

The present invention relates to an orally disintegrable tablet having a characteristic of fast disintegration in the oral cavity even without water.

BACKGROUND ART

Pharmaceutical solid preparations, for example, tablets, usually are prepared to make pharmaceutically active ingredients absorb in a digestive organ by disintegration or dissolution through oral administration, without fast disintegration or dissolution in the Qral cavityl

JP-A-6-502194 (U.S. Pat. No. 5,464,632) discloses a rapidly disintegrable multiparticulate tablet, the excipient mixture of which is suitable for imparting a disintegration rate such that the tablet disintegrates in the mouth in less than sixty seconds, characterized by the fact that the active substance is present in the form of coated microcrystals or coated or uncoated microgranules. However, there is no disclosure of an acid-labile physiologically active substance with a basic inorganic salt as the active substance, weight percentage of the active substance in the excipient mixture, or the size of the coated microgranule.

On the other hand, JP-A-5-92918 discloses a powder consisting of a fine-particle core coated with a water-soluble high molecular compound and at least one physiologically active substance, and having a granule size of practically up to 500 μm. However, there is no disclosure of an acid-labile physiologically active substance with a basic inorganic salt as the physiologically active substance, weight percentage of the active substance in the coated granule or the size of the coated granule.

JP-A-63-301816 and U.S. Pat. No. 5,026,560 disclose spherical granules having a core coated with spraying powder containing a drug and low substituted hydroxypropylcellulose. However, there is no disclosure of an orally disintegrable tablet.

EP-A-0452862 discloses a spherical granule obtained by coating a pharmacologically inactive spherical seed core having at least 50 weight % microcrystalline cellulose and an average particle size of 100–1000 μm, with a powder comprising an active ingredient, by using an aqueous binding solution, and spraying an aqueous solution or suspension of a coating agent thereon. However, most of the particle sizes of thus obtained granules are 500 μm or more.

JP-A-1-268627, JP-A-1-268628 and JP-A-8-27033 disclose pharmaceutical compositions using erythritol, respectively. However, there is no disclosure of a solid pharmaceutical composition characterized by fast disintegration in the oral cavity.

JP-A-9-48726 discloses a buccal formulation consisting of a drug and a substance wetting in a mouldable way on humidifying, and retaining a shape after moulding and drying. As such substance, sugars, sugar alcohols and water-soluble polymers are exemplified.

JP-A-5-271054 discloses production of fast dissolving tablets comprising an active ingredient and sugars.

JP-A-9-71523 discloses a tablet with rapid disintegration in the oral cavity comprising medicine, crystalline cellulose, low-substituted hydroxypropyl cellulose and lubricant.

However, these prior art references nowhere disclose an acid-labile physiologically active substance with a basic inorganic salt as an active substance, weight percentage of the active substance in the tablet or the size of the coated fine granule.

To accompany an aging population and their changes in life environment, it is desired to develop an orally disintegrable solid preparation capable of being administered without water, retaining the convenience for use which is a characteristic of a tablet, and being administered on demand easily, anytime and anywhere, without water.

Conventional granules have large particle diameters, which results in inferior workability when dispensing, and also results in difficulties in consistently adding a regular amount of the granules when they are combined into tablet or capsules. Granules having a large particle diameter (400 μm or more of average particle diameter) also produce a feeling of roughness in the mouth. Accordingly, especially when used in an orally disintegrable tablet, the average particle a diameter of the included granules must be about 400 μm or less, preferably about 350 μm.

For many reasons, such as, masking a bitter taste, or providing enteric abilities or release abilities, it is desirable to prepare the solid pharmaceutical preparations as granules (or fine granules), In particular, in case of granules or fine granules in which the active ingredient of the drug is enteric coated to impart enteric dissolution, there is a need for enteric coating to prevent dissolution by stomach acid (i.e., to make the preparation acid-resistance). It is necessary to coat the whole surface of the particle—before the enteric coating—(including a case of the crystal of physiologically active substance only, and a case of the granule produced by granulation), with the enteric coating. Namely, at least some uniform thickness (at least 20 μm or more) of the coating layer is needed. Even a portion of thin and weak coating, is undesirable because acid-resistance is lowered. Accordingly, before the enteric coating, it is necessary that the particle is as spherical with as smooth a surface as possible in form, as uniform as possible in size, and has less cavities.

It is very difficult to produce an enteric coated fine granule with an average particle diameter of 400 μm or less, when the coating is performed no that at least 20 μm thickness of coating layer may coat the whole particle, and the enteric coated particle contains a basic inorganic salt for stabilization of an acid-labile physiologically active substance, and where it contains binders for maintaining the strength of the particle and/or disintegrants for maintaining the disintegrability (dissolution) of the particles. Further, in the case where the content of the acid-labile physiologically active substance is increased, it is necessary to also increase the content of the excipients such as basic inorganic salt, binders and disintegrants. Furthermore, it is very difficult to produce a small enteric coated fine granule containing the physiologically active substance in high content.

Accordingly, it is desired to develop a fine granule which is coated with the enteric coating layer on the composition containing the physiologically active substance such as a physiologically active substance containing a basic inorganic salt and which has a particle diameter so that roughness or oral discomfort is not felt, to develop a fine granule containing the physiologically active substance, i.e., the active ingredients of drugs, and so forth, in high content, to develop a fine granule while maintaining enteric dissolution, a disintegrability and dissolution and suitable strength, and to develop an orally disintegrable preparation containing such a fine granule, being a fast disintegration type, showing

superior oral disintegrability and dissolution and having suitable strength (hardness) so that it will not be damaged through production processes or handling.

In particular, there is a need to combine an acid-labile physiologically active substance, with basic inorganic salts and so forth for stability, and further to coat with coating layers such as an enteric layer. In such cases, it is an important problem to produce an small enteric coated fine granule, even though it contains the acid-labile physiologically active substance in high concentration and in high content.

DISCLOSURE OF INVENTION

The present invention relates to:

[1] an orally disintegrable tablet which comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive;

[2] an orally disintegrable tablet of the above [1], wherein the average particle diameter of the fine granules is 300 to 400 μm;

[3] an orally disintegrable tablet of the above [1], wherein the fine granules further comprise a basic inorganic salt;

[4] an orally disintegrable tablet of the above [1], wherein the additive comprises a water-soluble sugar alcohol;

[5] an orally disintegrable tablet of the above [1], wherein the composition coated by an enteric coating layer is further coated by a coating layer which comprises a water-soluble sugar alcohol;

[6] an orally disintegrable tablet of the above [4], wherein the additive comprises (i) crystalline cellulose and/or (ii) low-substituted hydroxypropyl cellulose;

[7] an orally disintegrable tablet of the above [1], wherein the particle diameter of the fine granules is practically 425 μm or less;

[8] an orally disintegrable tablet of the above [1], wherein the particle diameter of the fine granules is practically 400 μm or less;

[9] an orally disintegrable tablet of the above [1], wherein the acid-labile physiologically active substance is a benzimidazole compound or a salt thereof;

[10] an orally disintegrable tablet of the above [9], wherein the benzimidazole compound is lansoprazole;

[11] an orally disintegrable tablet of the above [3], wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium;

[12] an orally disintegrable tablet of the above [1], wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose;

[13] an orally disintegrable tablet of the above [12], wherein the core comprises 50 weight % or more of lactose;

[14] an orally disintegrable tablet of the above [12], wherein the core comprises 40 to 50 weight % of crystalline cellulose and 50 to 60 weight % of lactose;

[15] an orally disintegrable tablet of the above [1], wherein the composition comprises 20 weight % or more of an acid-labile physiologically active substance;

[16] an orally disintegrable tablet of the above [1], wherein the composition comprises 20 to 50 weight % of an acid-labile physiologically active substance;

[17] an orally disintegrable tablet of the above [1], wherein the fine granules are produced by fluidized-bed granulation method;

[18] an orally disintegrable tablet of the above [1], wherein the enteric coating layer comprises an aqueous enteric polymer agent;

[19] an orally disintegrable tablet of the above [18], wherein the aqueous enteric polymer agent is a methacrylate copolymer;

[20] an orally disintegrable tablet of the above [18], wherein the enteric coating layer further comprises a sustained-release agent;

[21] an orally disintegrable tablet of the above [20], wherein the sustained-release agent is a methacrylate copolymer;

[22] an orally disintegrable tablet of the above [20], wherein the sustained-release agent is in an amount of 5 to 15 weight % relative to 100 weight % of the aqueous enteric polymer agent;

[23] an orally disintegrable tablet of the above [4], wherein the water-soluble sugar alcohol is erythritol;

[24] an orally disintegrable tablet of the above [4], wherein the water-soluble sugar alcohol is mannitol;

[25] an orally disintegrable tablet of the above [5], wherein the water-soluble sugar alcohol is in an amount of 5 to 97 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules;

[26] an orally disintegrable tablet of the above [4], wherein the crystalline cellulose is in an amount of 3 to 50 weight % relative to 100 weight % of the tablet apart from the fine granule;

[27] an orally disintegrable tablet of the above [6], wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropyl cellulose is 7.0 to 9.9 weight %;

[28] an orally disintegrable tablet of the above [6], wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropyl cellulose is 5.0 to 7.0 weight %;

[29] an orally disintegrable tablet of the above [1], which further comprises crospovidone;

[30] an orally disintegrable tablet of the above [1], wherein the oral disintegration time is one minute or less;

[31] an orally disintegrable tablet of the above [1], which comprises no lubricant inside the tablet;

[32] fine granules having an average particle diameter of 400 μm or less, which comprise a composition coated by an enteric coating layer, said composition having (i) 25 weight % or more of an acid-labile physiologically active substance and (ii) a basic inorganic salt;

[33] fine granules of the above [32], wherein the average particle diameter of the fine granules is 300 to 400 μm;

[34] fine granules of the above [32], wherein the particle diameter of the fine granules is practically 425 μm or less;

[35] fine granules of the above [32], wherein the particle diameter of the fine granules is practically 400 μm or less;

[36] fine granules of the above [32], wherein the acid-labile physiologically active substance is a benzimidazole compound or a salt thereof;

[37] fine granules of the above [36], wherein the benzimidazole compound is lansoprazole;

[38] fine granules of the above [32], wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium;

[39] fine granules of the above [32], wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose;

[40] fine granules of the above [39], wherein the core comprises 50 weight % or more of lactose;

[41] fine granules of the above [32], wherein the composition comprises 25 to 40 weight % of an acid-labile physiologically active substance;

[42] fine granules of the above [32], which are produced by fluidized-bed granulation method;

[43] fine granules of the above [32], wherein the enteric coating layer comprises an aqueous enteric polymer agent;

[44] fine granules of the above [43], wherein the aqueous enteric polymer agent is a methacrylate copolymer;

[45] fine granules of the above [43], wherein the enteric coating layer further comprise a sustained-release agent;

[46] fine granules of the above [45], wherein the sustained-release agent is a methacrylate copolymer;

[47] fine granules of the above [45], wherein the sustained-release agent is in an amount of 5 to 15 weight % relative to 100 weight % of the aqueous enteric polymer agent;

[48] fine granules of the above [32], wherein the enteric coating layer is in an amount of 50 to 70 weight % relative to 100 weight % of the fine granules;

[49] a tablet, granule, fine granule, capsule, effervescent or suspension preparation which comprises the fine granules of the above [32], and so forth.

In the present specification, "coating" means also partial coating and adhesion or adsorption in addition to coating the whole surface of an object (e.g., core) which is to be coated.

"Spherical" means also forms having a curved surface such as forms having elliptic cross sections, and forms in the shapes of eggplants and drops in addition to spheres.

"Average particle diameter" means volume based distribution median diameter (median diameter: 50% particle diameter from cumulative distribution), unless otherwise specified. It can be measured by, for example, a laser diffraction particle distribution measurement method. Concretely exemplified is a method using Raser Diffraction Analyzer, type: HEROS RODOS [trade name; manufactured by Sympatec (Germany)].

"An orally disintegrable tablet" of the present invention comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive.

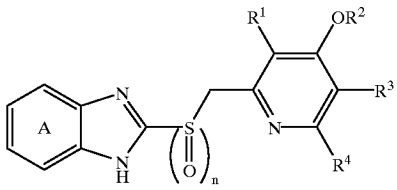
In the present invention, "fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance" have an average particle diameter of about 400 μm or less, in order that roughness is not felt in the mouth. Preferably, the average particle diameter of the fine granules is 300 to 400 μm.

Aside from the average particle diameter of the above "fine granules", regarding the maximum particle size, the particle diameter is practically 425 μm or less, and preferably practically 400 μm or less. Preferably, the particle diameter is practically 300 to 425 μm, more preferably 300 to 400 μm.

"Practically" as used in "the particle diameter is practically 425 μm or less" and "the particle diameter is practically 400 μm or less" means that the particles may include a small quantity (about 5 weight % or less) of particles whose particle diameter Is out of above described range to Include the inevitable contaminant particles.

"An acid-labile physiologically active substance" includes a compound being unstable in an acidic region and/or a compound inactivated by an acid, especially a pharmaceutical ingredient. Concretely mentioned are vitamins such as vitamin B_{12}, fursultiamine, folic acid, vitamin A, vitamin D, as well as a known benzimidazole compound having an antiulcer activity of the formula (I) below, or a salt thereof.

Formula (I)



wherein ring A may be substituted; R^1, R^3 and R^4 are the same or different and each is a hydrogen, an alkyl or an alkoxy; R^2 is C_{1-4} alkyl which may be substituted by a substituent(s) selected from the group consisting of halogen, hydroxy and C_{1-4} alkoxy; and n is 0 or 1.

In the above formula (I), "substituent(s)" of the "substituted ring A" include, for example, halogen, C_{1-10} alkyl which may be substituted, C_{3-7} cycloalkyl which may be substituted, C_{2-16} alkenyl which may be substituted, C_{1-10} alkoxy which may be substituted, cyano, carboxy, C_{1-7} alkoxycarbonyl, C_{1-4} alkoxycarbonyl-C_{1-4} alkyl, carbamoyl, carbamoyl-C_{1-14} alkyl, hydroxy, hydroxy-C_{1-7} alkyl, C_{1-6} acyl, carbamoyloxy, nitro, C_{2-6} acyloxy, C_{6-12} aryl, C_{6-12} aryloxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, etc.

The "substituent" of the above "C_{1-10} alkyl which may be substituted", "C_{3-7} cycloalkyl which may be substituted", or "C_{2-16} alkenyl which may be substituted" includes, for example, (1) halogen, (2) nitro, (3) amino which may be substituted by 1 or 2 of C_{1-4} alkyl and C_{1-4} acyl, etc., (4) amidino, (5) guanidino, (6) carbamoyl, etc. The number of these substituents is 1 to 3.

The "substituent" of the above "C_{1-10} alkoxy which may be substituted" includes, for example, (1) halogen, (2) nitro, (3) amino which may be substituted by 1 or 2 of C_{1-4} alkyl and C_{1-4} acyl, etc., (4) amidino, (5) guanidino, etc. The number of these substituents is 1 to 3.

The above "C_{1-6} acyl" includes, for example, C_{2-6} alkanoyl such as formyl, acetyl, propionyl, etc.

The above "C_{1-4} acyl" includes, for example, formyl and C_{2-4} alkanoyl such as acetyl, propionyl, etc.

The above "C_{2-6} acyloxy" includes, for example, C_{2-6} alkanoyloxy such as acetyloxyl, etc.

The above "C_{6-12} aryl" includes, for example, phenyl, naphthyl, etc.

The above "C_{6-12} aryloxy" includes, for example, phenoxy, naphthyloxy, etc.

The "alkyl" for R^1, R^3 or R^4 includes, for example, a straight-chain or branched C_{1-10} alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl,

decyl, etc. Among others, preferred is a straight-chain or branched C_{1-6} alkyl. More preferred is a straight-chain or branched C_{1-3} alkyl.

The "alkoxy" for R^1, R^3 or R^4 includes, for example, C_{1-10} alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, cyclobutoxy, cyclopentoxy, cyclohexyloxy, etc. Among others, preferred is C_{1-6}alkoxy. More preferred is C_{1-3} alkoxy.

The "C_{1-4} alkyl" of the "C_{1-4} alkyl which may be substituted by a substituent(s) selected from the group consisting of halogen, hydroxy and C_{1-4} alkoxy" for R^2 includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, etc.

The "C_{1-4} alkoxy" of the above "C_{1-4} alkyl which may be substituted by a C_{1-4} alkoxy" includes, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.

The number of the substituents which the "C_{1-4} alkyl" has is preferably 1 to 3.

Salts of the benzimidazole compound include pharmaceutically acceptable salts such as alkali metal salts, e. g., sodium salts and potassium salts, alkaline earth metal salts e. g., calcium salts and magnesium salts, etc.

Such benzimidazole compounds having an antiulcer activity, or salts thereof include, for example, a compound or a salt thereof disclosed in JP-A-52-62275, JP-A-54-141783 JP-A-57-53406, JP-A-58-135881, JP-A-58-192880, JP-A-59-181277, JP-A-61-50978, JP-A-62-116576, JP-A-62-277322, JP-A-62-258320, JP-A-62-258316, JP-A-64-6270, JP-A-64-79177, JP-A-5-59043, JP-A-62-111980, JP-A-5-117268, EP-A-166287, EP-A-519365, and so forth.

The "physiologically active substance" of the present invention preferably is a benzimidazole compound or a salt thereof such an tenooprdzole, omneirazole, rabmprazole, pantoprazole, perprazole, leminoprazole, TU-199, etc. Preferred is lansoprazole and omeprazole, etc. More preferred is lansoprazole.

The amount of the "acid-labile physiologically active substance" in the "composition" is, for example, about 10 weight % or more, preferably about 20 weight % or more, more preferably about 23 weight % or more, especially preferably about 25 weight % or more. Among others, preferred is 20 to 50 weight %.

In the "composition", a basic inorganic salt is preferably incorporated with the acid-labile physiologically active substance.

The "basic inorganic salt" includes, for example, a basic inorganic salt of sodium, potassium, magnesium and/or calcium, preferably a basic inorganic salt of magnesium and/or calcium. Among others, preferred is a basic inorganic salt of magnesium.

The basic inorganic salt of sodium includes, for example, sodium carbonate, sodium hydrogencarbonate, etc.

The basic inorganic salt of potassium includes, for example, potassium carbonate, potassium hydrogencarbonate, etc.

The basic inorganic salt of magnesium includes, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metagilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite [$Mg_6Al_2(OH)_{16}.CO_3.4H_2O$], aluminum magnesium hydroxide [$2.5MgO.Al_2O_3.xH_2O$], etc. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc.

The basic inorganic salt of calcium includes, for example, precipitated calcium carbonate, calcium hydroxide, etc.

The preferable examples of the "basic inorganic salt" include heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc.

Such basic inorganic salt of magnesium or calcium, etc. has a basic pH (not less than 7) when it is in the form of a 1% aqueous solution or suspension.

Two or more of these basic inorganic salts (preferably a basic inorganic salt of magnesium, a basic inorganic salt of calcium, etc.) can be used as a mixture in a given ratio. The amount of the basic inorganic salt to be used is appropriately selected depending on the kind of the basic inorganic salt and is, for instance, about 0.3 to 200 weight %, preferably about 1 to 100 weight %, more preferably about 10 to 50 weight %, especially preferably about 20 to 40 weight % relative to the benzimidazole compound or a salt thereof.

The "composition" may contain water-soluble polymers, the following binders, lubricants, and excipients, etc. in common use as pharmaceutical materials. The amount of such water-soluble polymers, binders, lubricants, and excipients is selected from amounts commonly employed in the manufacture of preparations in general dosage forms.

The "water-soluble polymer" includes, for example, a water-soluble polymer which is soluble in ethanol (i.e., an ethanol-soluble water-soluble polymer) such as a cellulose derivative (e.g., hydroxypropyl cellulose, which may be referred to as "HPC" hereinafter), poly(vinylpyrrolidone), etc.; a water-soluble polymer which is insoluble in ethanol (i.e., an ethanol-insoluble water-soluble polymer) such as a cellulose derivative (e.g., hydroxypropylmethyl cellulose, which may be referred to as "HPMC" hereinafter, methyl cellulose, carboxymethyl cellulose sodium, etc.), sodium polyacrylate, polyvinyl alcohol, sodium alginate, and guar gum, etc.

When such water-soluble polymers are used, the dissolution of drugs (physiologically active substances) can be controlled by employing them in combination with the ethanol-soluble water-soluble polymer and ethanol-insoluble water-soluble polymer or by employing them in combination with some water-soluble polymers having different viscosity.

In the present invention, the "water-soluble polymer" is preferably, a cellulose derivative such as HPC, HPMC, and methyl cellulose, and polyvinyl alcohol. More preferred is a cellulose derivative such as HPC, HPMC.

The "HPC" contains, for example, about 53.4 to 77.5 weight %, more preferably about 60 to 70 weight %, of hydroxypropoxyl group. The viscosity of 2 weight % aqueous solution of HPC at 20° C. is usually about 1 to 150,000 cps (centipoise). As the above HPC, hydroxypropyl cellulose defined in Japanese Pharmacopoeia may be employed. Hereinafter, all viscosity of HPC is a value of 2 weight % aqueous solution at 20° C.

The "HPMC" is a mixed ether which is connected by a methoxy group and a hydroxypropoxy group. The content of the methoxy group of HPMC is, for example, about 19 to 30 weight %, The content of the hydroxypropoxy group is, for example, about 4 to 12 weight %. The viscosity of 2 weight % aqueous solution of HPMC at 20° C. is usually about 1 to 40,000 centistokes. As such HPMC may be employed hydroxypropylmethyl cellulose 2208 defined by Japanese Pharmacopoeia, hydroxypropylmethyl cellulose 2906 defined by Japanese Pharmacopoeia, hydroxypropylmethyl cellulose 2910 defined by Japanese Pharmacopoeia, and so forth. Hycroxypropyl cellulose(s) may be employed alone or in admixture of two or more thereof.

The content of the water-soluble polymer such as HPC and/or HPMC is usually about 0.1 to 50 weight %, preferably about 1 to 30 weight %, as against the whole "composition" containing the physiologically active substance, in order to control the dissolution of the physiologically active substance in the composition containing the physiologically active substance and retain a high content of the physiologically active substance.

The above "enteric coating layer" which coats the "composition having 10 weight % or more of an acid-labile physiologically active substance" includes, for example, an aqueous enteric polymer agent such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate (hereinafter, referred to as HP-55), hydroxymethyl cellulose acetate succinate, methacrylate copolymer [e.g., Eudragit L30D-55 etc. (trade name; manufactured by Rohm GmbH (Germany)), KollICoat MAE30DP (trade name; manufactured by BASF (Germany)), Polyquid PA-30 (trade name; manufactured by SanyoKasei (Japan)), etc.], carboxymethyl cellulose, shellac, etc.; a sustained-release agent such as methacrylate copolymer [e.g., Eudragit NE30D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.]; a water-soluble polymer; plasticizers such as triethyl citrate, polyethylene glycol, acetylatedmonoglyceride, triacetin, castor oil, etc. and mixtures thereof.

The "aqueous enteric polymer agent" is preferably a methacrylate copolymer. The "sustained-release agent" is preferably a methacrylate copolymer.

The "sustained-release agent" is used in an amount of 5 to 30 weight %, preferably 5 to 15 weight %, relative to 100 weight % of the "aqueous enteric polymer agent". The "plasticizers" is used in an amount of 5 to 30 weight% relative to 100 weight % of the "aqueous enteric polymer agent".

The "additives" of the "orally disintegrable tablet which. comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive" may be ones commonly employed as pharmaceutical materials. The amount of such additives to be used is selected from amounts commonly employed in the manufacture of preparations in general dosage forms.

The "additives" include, for example, a water-soluble sugar alcohol, a crystalline cellulose, a low-substituted hydroxypropyl cellulose, as well as, binders, acids, foaming agents, artificial sweeteners, flavorants, lubricants, colorants, stabilizers, excipients, disintegrants, and so forth.

The "water-soluble sugar alcohol" means a water-soluble sugar alcohol which needs water in an amount of less than 30 ml when 1 g of water-soluble sugar alcohol is added to water and dissolved within about 30 minutes at 20° C. by strongly shaking every 5 minutes for 30 seconds.

The "water-soluble sugar alcohol" includes, for example, sorbitol, mannitol, maltitol, reduced starch saccharide, xylitol, reduced paratinose, erythritol, etc. Two or more of these water-soluble sugar alcohols can be used as a mixture in a given ratio.

The "water-soluble sugar alcohol" is preferably mannitol, xylitol and erythritol. More preferred is mannitol and erythritol. Especially preferred is mannitol. As erythritol, one that is produced by fermentation with yeasts using glucose as the starting material, and that has a particle size of at most 50 mesh is used. Such erythritol is available on the market, e.g. as manufactured by Nikken Chemical Co., Ltd. (Japan).

The "water-soluble sugar alcohol" is usually employed in an amount of about 5 to 97 weight %, preferably about 10 to 90 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules, in order to obtain sufficient strength of the preparation and sufficient disintegration or dissolution in the oral cavity.

For example, mannitol or erythritol is usually employed in an amount of about 5 to 90 weight %, preferably about 10 to 80 weight %, more preferably about 20 to 80 weight %, especially preferably about 50 to 80 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

The "crystalline cellulose" includes refined one having partially α-cellulose depolymerization. Such crystalline cellulose includes one called microcrystalline cellulose. Examples of the "crystalline cellulose" include CEOLUS KG801, avicel PH101, avicel PH102, avicel PH301, avicel PH302, avicel RC-591 (crystalline cellulose carmellose sodium), etc. Among these, preferably employed is CEOLUS KG801 which is also called crystalline cellulose of high compressibility. Two or more of the crystalline cellulose can be used as a mixture in a given ratio. Such crystalline cellulose is available on the market, for example, as manufactured by Asahi Chemical Co., Ltd. (Japan).

The "crystalline cellulose" is used, for instance, in an amount of about 3 to 50 weight %, preferably about 5 to 40 weight %, more preferably about 5 to 20 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

The "low-substituted hydroxypropyl cellulose" means a low-substituted hydroxypropyl cellulose wherein the content of hydroxypropoxyl group in the hydroxypropyl cellulose (hereinafter,maybe abbreviated to "the content of HPC group") is about 5.0 to 9.9 weight %, preferably a low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 5.0 to 7.0 weight %, a low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 7.0 to 9.9 weight %, and so forth.

The "low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 7.0 to 9.9% includes, for example, LH-22, LH-32 and mixtures thereof, which are commercially available [Shin-Etsu Chemical Co., Ltd. (Japan)]. Also, they can be produced in accordance with per se known methods, for example, methods described in JP-B-82 53100 or analogous thereto.

The low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 5.0 to 7.0% includes, for example, LH-23, LH-33 and mixtures thereof, described in the following Reference Examples. They can be produced in accordance with per se known methods, for example, methods described in JP-B-82 53100 or analogous thereto.

At first, alkaline cellulose containing free alkaline and propylene oxide is reacted to obtain the crude low-substituted hydroxypropyl cellulose containing free alkaline.

Concretely, for example, raw material pulp such as wood pulp and cotton leader is immersed in about 10 to 50% concentration of an aqueous solution of sodium hydroxide, and pressed to obtain alkaline cellulose of which NaOH/cellulose ratio is about 0.1 to 1.2 (ratio by weight). Next, crude low-substituted hydroxypropyl cellulose containing free alkaline is obtained by reacting the resulting alkaline cellulose and propylene oxide with stirring at about 20 to 90° C. for about 2 to 8 hours. Propylene oxide is used in an amount so that the content of hydroxypropoxyl group in the desired low-substituted hydroxypropyl cellulose can be 5 or more weight % to less than 7 weight % (in case of the

low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 5.0 to 7.0 weight %), 7 or more weight % to less than 9.9 weight % (in case of the low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 7.0 to 9.9 weight %).

The crude low-substituted hydroxypropyl cellulose containing free alkaline is dispersed in water or hot water containing about 5 to 80% of acid necessary to neutralize all the alkaline, and a part of the crude low-substituted hydroxypropyl cellulose containing free alkaline is dissolved therein. Acid is further added to neutralize the remaining alkaline.

After the neutralization, some processes such as drainage, drying and grinding are performed in accordance with conventional methods to obtain the desired low-substituted hydroxypropyl cellulose.

The particle diameter of "the low-substituted hydroxypropyl celluloses wherein the content of hydroxypropoxyl group is 5.0 to 7.0 weight %" to be used in the present invention is, for example, about 5 to 60 Sm. preferably about 10 to 40 μm, as a average particle diameter.

In the above ranges, in case that low-substituted hydroxypropyl celluloses (L-HPC) having a relatively large particle diameter (for example, L-HPC having about 26 to 40 μm of the average particle diameter) is employed, a pharmaceutical preparation superior in disintegrability can be produced. On the other hand, in case that L-HPC having a relatively small particle diameter (for example, L-HPC having about 10 to 25 μm of the average particle diameter) is employed, a pharmaceutical preparation superior in strength of the preparation can be produced. Accordingly, the particle diameter of L-HPC can be suitably selected according to the characteristics of the desired pharmaceutical preparation.

The "low-substituted hydroxypropyl cellulose wherein the content of HPC group is 5.0 to 7.0 weight %" or the "low-substituted hydroxypropyl cellulose wherein the content of HPC group is 7. 0 to 9.9%" is usually employed in an amount of about 3 to 50 weight %, preferably about 5 to 40 weight %, relative to 100 weight % of the orally disintegrable tablet apart from the fine granules, in order to obtain sufficient oral disintegrability and sufficient strength of the preparation.

The "binders" include, for example, hydroxypropyl cellulose, hyaroxypropylmethylcellulose, crystalline cellulose, α starch (pregelatinized starch), polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan, low-substituted hydroxypropyl cellulose, etc. The use of crystalline cellulose as the binders provides a solid preparation which exhibits more excellent strength of a preparation while retaining excellent disintegration and dissolution in the oral cavity.

The "acids" include, for example, citric acid (e.g., citric acid anhydrous), tartaric acid, malic acid, etc.

The "foaming agents" include, for example, sodium hydrogen carbonate, etc.

The "artificial sweeteners" include, for example, saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia, thaumatin, etc.

The "flavorants" include synthetic flavorants or natural flavorants, such as lemon, lime, orange, menthol, strawberry, etc.

The "lubricants" include, for example, magnesium stearate, sucrose fatty acid ester, polyethyleneglycol, talc, stearic acid, etc.

The "colorants" include, for example, various food colorants such as Food Yellow No. 5, Food RED No. 2, Food Blue No. 2, etc., food lakes, red iron oxide, etc.

The "stabilizers" include, for example, the above-mentioned "basic inorganic salt".

The "excipients" include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride, titanium oxide, etc.

The "disintegrants" include those conventionally used in the pharmaceutical field, such as (1) crospovidone, (2) super disintegrants such as croscarmellose sodium [FMC-Asahi Chemical Co., Ltd. (Japan)], carmellose calcium [Gotoku Chemical(Yakuhin), (Japan)], (3) carboxymethylstarch sodium [e.g., Matsutani Chemical Co., Ltd. (Japan)], (4) low-substituted hydroxyDropyl cellulose e.g., Shin-Etgu Chemical Co., Ltd. (Japan)], (5) corn starch, etc. Among others, preferred is, for example, crospovidone.

The "crospovidone" includes polyvinylpolypyrrolidone (PVPP), 1-vinyl-2-pyrrolidinone homopolymer, 1-ethenyl-2-pyrrolidinone homopolymer, etc, such as Kollidon CL [manufactured by BASF (Germany)], Polyplasdone XL [manufactured by ISP Ltd. (Japan)], Polyplasdone XL-10 [manufactured by ISP Ltd. (Japan)], Polyplasdone INF-10 [manufactured by ISP Ltd. (Japan)], etc. Usually crospovidone having a molecular weight of at least 1,000,000 is used.

Two or more of these disintegrants can be as a mixture in a given ratio. For example, (i) crospovidone solely, or (ii) crospovidone and another disintegrant(s) is preferably employed.

The "disintegrants" are used, for instance, in an amount of about 1 to 15 weight %, preferably about 1 to 10 weight %, more preferably about 3 to 7 weight %, relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

In the present invention, the "fine granules" may contain, for example, titanium oxide as a masking agent.

The diameter of the "orally disintegrable tablet" of the present invention is about 5 to 20 mm, preferably about 7 to 15 mm, more preferably about 8 to 13 mm.

The "orally disintegrable tablet" may comprise no lubricant inside the tablet.

The "orally disintegrable tablet" of the present invention exhibits fast disintegrability or dissolubility in the oral cavity, and also an appropriate strength of preparation.

The oral disintegration time of the "orally disintegrable tablet" of the present invention (the time for healthy male or female adults to complete disintegration by buccal saliva) is one minute or less, usually about 50 seconds or less, preferably about 40 seconds or less, more preferably about 30 seconds or less.

The strength of the "orally disintegrable tablet" of the present invention (measurement with a tablet hardness tester) is usually about 1 to 20 kg, preferably about 2 to 15 kg, more preferably 3 to 8 kg.

In the above-mentioned fine granules, "fine granules having an average particle diameter of 400 pzn or less, which comprise a composition coated by an enteric coating layer, said composition having (i) 25 weight % or more of an acid-labile physiologically active substance and (ii) a basic inorganic salt" are novel.

The "fine granules" have an average particle diameter of about 400 μm or less, preferably 350 μm or less. Preferably; the average particle diameter of the fine granules is 300 to 400 μm. Aside from the average particle diameter of the "fine granules", regarding the maximum particle size, the particle diameter is practically 425 μm or less, and preferably practically 400 μm or less. Preferably, the particle diameter is practically 300 to 400 μm or less.

Regarding the fine granule of the present invention, the dissolution of the physiologically active substance can be

controlled by formulating the coat (coating layer) to have different viscosity or content of the water-soluble polymer (e.g., HPC, HPMC and so forth) or by formulating the coat to have a controlled ratio of the ethanol-soluble water-soluble polymer (e.g., HPC) and the ethanol-insoluble water-soluble polymer (e.g., HPMC). The dissolution of the physiologically active substance is not very influenced by liquidity, which can be suitably controlled.

As a pharmaceutical preparation which comprises the "fine granules" of the present invention, there may be employed, for example a solid preparation such as tablet, granule, fine granule, capsule, effervescent, etc; a liquid preparation such as suspension preparation, etc. Among others, preferred is a tablet, more preferred is an orally disintegrable tablet.

When the "fine granule" of the present invention is used for a tablet except for an orally disintegrable tablet, the diameter of the tablet is about 5 to 10 mm, preferably about 5 to 8 mm. When the fine granule of the present invention is used for a capsule, the size of the capsule is preferably a #2 capsule or less.

The "orally disintegrable tablet" of the present invention is and the "pharmaceutical preparation which comprises the fine granules of the present invention" may contain a foaming component to impart a refreshing feeling at administration. Also, with an effervescent comprising the foaming component, the dissolution can be precisely controlled compared to the case of a fine granule alone. As the foaming component, various compounds can be employed as long as safety is not interfered with. Examples of the foaming component include alkaline metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkaline metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.) and ammonium carbonate and so forth. The foaming component(s) may be employed alone or in an admixture of two or more thereof. The preferable foaming component includes sodium carbonate, sodium hydrogencarbonate, ammonium carbonate and so forth. The ratio of the foaming component can be selected within the range in which it is possible to impart the foam, for example, about 10 to 2500 weight %, preferably about 50 to 2000 weight % (e.g., about 75 to 1500 weight %), more preferably about 100 to 1000 weight %, relative to 100 weight % of the fine granule.

In employing the effervescent and the fine granule having small particle diameter, it is advantageous to quickly prepare a homogeneous aqueous solution or suspension, and to maintain the dispersed condition. But, in case that the particle diameter is too small, the problem tends to occur that the fine granule adheres to the wall of a machine by static electricity during production processes.

The specific volume of the above fine granule is about 3 ml/g or less, preferably about 2 ml/g or less. In order to maintain the homogeneous condition of the fine granule in the suspension obtained by adding the foaming agent composition, the specific volume can be suitably selected in the above range according to the specific gravity (specific volume) of the dispersion medium.

The "composition" in the present invention can be produced by a known granulation method.

The "granulation method" includes, for example, rolling granulation method (e.g., centrifugal rolling granulation, etc.), fluidized-bed granulation (e.g., rolling fluidized bed granulation, fluidized granulation, etc.), stirring granulation and so forth. Among others, preferred is fluidized-bed granulation method, more preferred is rolling fluidized-bed granulation method.

Concrete example of the "rolling granulation method" includes a method using "CF apparatus" manufactured by Freund Industrial Co., Ltd. (Japan) and so forth. Concrete examples of the "rolling fluidized-bed granulation method" include methods using "SPIR-A-FLOW", "multi plex" manufactured by Powrex Corp. (U.S.A.), "New-Marumerizer" manufactured by Fuji Paudal Co., Ltd. (Japan), and so forth. The method for spraying the mixture can be suitably selected in accordance with the kind of granulator, and may be, for example, any one of a top spray method, a bottom spray method, a tangential spray method, and so forth. Among others, a tangential spray method is preferred.

The "composition" in the present invention. can be produced in accordance with, for example, a method which comprises coating a core comprising crystalline cellulose and lactose with an acid-labile physiologically active substance.

For example, employed is a method described in JP-A-5-92918 (coating method), which comprises coating a core comprising crystalline cellulose and lactose with an acid-labile physiologically active substance, if necessary together with a basic inorganic salt, binders, lubricants, excipients, a water-soluble polymer, etc. (hereinafter, may be abbreviated to "coating layer"). For example, employed is a method which comprises coating a core with an acid-labile physiologically active substance and a basic inorganic salt, and then further with binders, lubricants, excipients, a water-soluble polymer, etc.

The average particle diameter of the "cores" is about 250 μm or less, preferably about 50 to 250 μm, more preferably about 100 to 250 μm, especially preferably about 100 to 200 μm. The "cores" having the above average particle diameter include particles which all pass through a #50 sieve (300 μm), particles where about 5 w/w % or less of the total remain on a #60 sieve (250 μm), and particles where about 10 w/w % or less of the total pass through a #282 sieve (53 μm) The specific volume of the "core" is about 5 ml/g or less, preferably about 3 ml/g or less.

Examples of the "core" include

(1) a spherical granulated product comprising crystalline cellulose and lactose, (2) a spherical granulated product being about 150 to 250 μm and comprising crystalline cellulose (avicel SP, manufactured by Asahi Chemical Co., Ltd. (Japan)), (3) a stirring granulated product being about 50 to 250 μm and comprising lactose (9 parts) and a starch (1 part), (4) a micro particle being about 250 μm or less classified as a spherical granule comprising micro crystalline cellulose described in JP-A-61-213201, (5) a processed product such as wax formed to a sphere by spraying or melting granulation, (6) a processed product such as gelatin beads comprising oil component, (7) calcium silicate, (8) starch, (9) a porous particle such as chitin, cellulose, chitosan, etc, and (10) a bulk product such as granulated sugar, crystalline lactose or sodium chloride, and processed preparations thereof. Further, these cores may be produced in accordance with per se known grinding method or granulation method, and sifted to prepare the particles having the desired particle diameter.

The above "spherical granulated product comprising crystalline cellulose and lactose" includes, for example (i) a spherical granulated product being 100 to 200 μm and comprising crystalline cellulose (3 parts) and lactose (7 parts) [e.g., Nonpareil 105 (70–140) (particle diameter of 100 to 200 μm), manufactured by Freund Industrial Co., Ltd. (Japan)], (ii) a spherical granulated product being about 150

to 250 μm and comprising crystalline cellulose (3 parts) and lactose (7 parts) [e.g., Nonpareil NP-7:3, manufactured by Freund Industrial Co., Ltd. (Japan)], (iii) a spherical granulated product being 100 to 200 μm and comprising crystalline cellulose (4.5 parts) and lactose (5.5 parts) [e.g., Nonpareil 105T (70–140) (particle diameter of 100 to 200 μm), manufactured by Freund Industrial Co., Ltd. (Japan)], (iv) a spherical granulated product being about 150 to 250 μm and comprising crystalline cellulose (5 parts) and lactose (5 parts) [e.g., Nonpareil NP-5:5, manufactured by Freund Industrial Co., Ltd. (Japan)], and so forth.

In order to produce a pharmaceutical preparation which is superior in dissolution while retaining suitable strength, the "core" includes, for example, preferably the spherical granulated product comprising crystalline cellulose and lactose, more preferably the spherical granulated material comprising crystalline cellulose and lactose and containing 50 weight % or more of lactose. Among others, preferred in a core comprising 40 to 50 weight % of crystalline cellulose and 50 to 60 weight % of lactose.

As the "core" employed in the present invention, in particular, there may be employed the spherical granulated product comprising crystalline cellulose and lactose, more preferably the spherical granulated product with a diameter of about 100 to 200 μm and comprising crystalline cellulose (4.5 parts) and lactose (5.5 parts).

The "core" may contain the physiologically active substance such as the above described pharmaceutical ingredient. Also, the "core" may not contain the physiologically active substance because the release of the physiologically active substance can be controlled by a coating layer containing the physiologically active substance.

The "core" is preferably as uniform a sphere as possible, for reducing the irregularity of the coating, in addition to being a powdery core.

The ratio of the "coating layer" to the "core" can be selected within the range in which it is possible to control dissolution of the physiologically active substance and particle size of the composition, for example, usually about 50 to 400 weight % relative to 100 weight % of the core.

The coating layer may be constructed by plural layers. At least one layer of the plural layers must contain the physiologically active substance. The combination of various layers such as a coating layer not containing the active ingredient, a base coating layer, and an enteric coating layer which constitute the coating layer can be suitably selected.

In case that the "core" is coated, for example, the above physiologically active substance and the water-soluble polymer can be employed in admixture thereof. The admixture may be a solution or a dispersion, and can be prepared by using an organic solvent such as water or ethanol or an admixture thereof.

The concentration of the water-soluble polymer in the admixture varies according to the ratio of the physiologically active substance and the excipients, and is usually about 0.1 to 50 weight %, preferably about 0.5 to 10 weight %, in order to retain the binding strength of the physiologically active substance to the core and maintain the viscosity of the mixture so as not to reduce the workability.

Where the coating layer comprises plural layers, the concentration of the physiologically active substance in each layer may be changed successively or gradually by selecting for the content ratio or viscosity of the water-soluble polymer or by successive coating with mixtures varying in the ratio of the physiologically active substance and the other excipients. In the above case, it may be coated with a mixture in which the content ratio of the water-soluble polymer is out of the range of about 0.1 to 50 weight %, as long as the coating layer as a whole contains about 0.1 to 50 weight % of the water-soluble polymer. Further, in forming the inactive coat according to known methods, the coating layer may comprise some layers such that the inactive layer may block each layer containing the physiologically active substance.

Also, in case of two or more physiologically active substances not suited in the compatibility, the core may be coated by employing each mixture together or separately.

The above coated material is dried, and passed through sieves to obtain a "composition" having uniform size. Because the form of the powder is usually according to the core, a fine granule being in the form of a rough sphere may be obtained. As the sieve may be employed, for example a #50 circular sieve (3001 μm). The composition is obtained by selecting those which pass through the #50 circular sieve.

The "fine granule" in the present invention can be produced in accordance with in the same manner as above granulation method, for example, a method which comprises coating the composition with an enteric coating layer, in order to protect the acid-labile physiologically active substance or to impart enteric dissolution. If necessary, the composition coated with an enteric coating layer may be further coated by a water-soluble sugar alcohol, preferably mannitol. In such case, the strength of the orally disintegrable tablet comprising fine granules is improved.

The "enteric coating layer" is preferably a layer having about 20 to 70 μm, preferably about 30 to 50 μm of thickness and coating the whole surface of the composition containing the physiologically active substance. Accordingly, the smaller particle diameter of the composition, the higher the weight % of the enteric coating layer in the whole fine granule. In the fine granule of the present invention, the "enteric coating layer" is about 30 to 70 weight %, preferably about 50 to 70 weight %, of the fine granule as a whole.

The "enteric coating layer" may be constructed by plural (e.g., 2 or 3) layers. For example, employed is a method which comprises coating a composition with an enteric coating layer having polyethyleneglycol, and then with an enteric coating layer having triethyl citrate, followed by being coated with an enteric coating layer having polyethyleneglycol.

The "orally disintegrable tablet" of the present invention can be produced in accordance with a conventional method in the pharmaceutical field. Such methods include, for instance, a method which comprises blending the "fine granules" and the "additives", and molding, if necessary followed by drying. Concretely mentioned is a method which comprises blending the fine granules and the additives, if necessary with water, and molding, if necessary followed by drying.

The "blending procedure" can be carried out by any of the conventional blending techniques such as admixing, kneading, granulating, etc. The above "blending procedure" is carried out, for instance, by using an apparatus such as Vertical Granulator GV10 [manufactured by Powrex Corp. (Japan)], Universal Kneader [manufactured by Hata Iron Works Co., Ltd. (Japan)], fluidized bed granulator LAB-1 and FD-3S [manufactured by Powrex Corp. (Japan)], V-shape mixer, tumbling mixer, and so forth.

Preferred example of the method for the "orally disintegrable tablet" of the present invention is a method which comprises:

(i) coating a core comprising crystalline cellulose and lactose with an acid-labile physiologically active substance and a basic inorganic salt, followed by being

coated with a coating layer comprising a water-soluble polymer to obtain a composition,

(ii) coating the resultant composition with an enteric coating layer having polyethyleneglycol, and then with an enteric coating layer having triethyl citrate, and then with an enteric coating layer having polyethyleneglycol, followed by being coated by mannitol to obtain fine granule, and

(iii) blending the resultant fine granule with an additive, followed by molding.

Where the pharmaceutical preparation of the present invention, especially an orally disintegrable tablet, is one which comprises no lubricant inside the preparation or tablet, such preparation can be preferably produced in accordance with methods described in JP-A-56-14098, Japanese Patent No. 2681601, etc. Such preparation, especially an orally disintegrable tablet, has sufficient strength. The above lubricant includes, for example, magnesium stearate, sucrose fattyacid ester, polyethyleneglycol, talc, stearic acid, etc.

The pharmaceutical preparations such as solid preparation (e.g., tablets, granules, fine granules, capsules, effervescents, etc.) and liquid preparation such as suspending preparation, which comprises the "fine granules" of the present invention can be produced in accordance with a conventional method.

The solid pharmaceutical preparation containing the "fine granules" of the present invention and the "orally disintegrable tablet" of the invention can also be produced by the wet tabletting method. As the above method, it is preferably employed the methods described in JP-A-5-271054 and so forth. They can also be produced by drying after humidification. As the above method, preferably employed are the methods described in JP-A-9-48726, JP-A-8-291051 and so forth. Namely, it is effective to humidify before tabletting or after tabletting and then to dry, in order to enhance the hardness.

The "molding procedure" can be carried out, for instance, by tabletting with a pressure of 0.5 to 3 ton/cm^2, preferably 1 to 2 ton/cm^2 by using a single-punch tabletting machine [Kikusui Seisakusho (Japan)] or a rotary type tabletting machine [Kikusui Seisakusho (Japan)] when a solid preparation is a tablet, especially an orally disintegrable tablet.

The "drying procedure" can be carried out by any of the techniques used commonly in the art, such as vacuum drying, fluidized-bed drying, etc.

The "fine granules" of the invention can be used for a pharmaceutical preparation. The pharmaceutical preparation includes, for example, a solid preparation such as tablet, granule, fine granule, capsule, effervescent, etc.; a liquid preparation such as a suspension preparation, etc. Among others, a tablet is preferred. Such tablet preferably has suitable strength so as to be stable through production processes and distributions.

A solid pharmaceutical preparation comprising the fine granule of the invention is used for an orally disintegrable tablet and can be administered without water or together with water.

As administration methods, there are listed (1) a method of administration by dissolution or disintegration together with a little water, or without water and with saliva in the oral cavity, not to be swallowed as it is, or (2) a method of administration with water, where it is swallowed as it is. Also, the tablet may be administered dissolved or disintegrated with water.

The "orally disintegrable tablet" of the present invention is advantageously used in (a) cases where administration without water is necessary, (b) cases of administration to a patients who have difficulty in swallowing tablets, or (c) cases of administration to the aged or to children where there is a fear of blocking the throat if it is in usual tablet form.

In case of the above (a), the orally disintegrable tablet is preferably used for antipyretic agents, analgesic agents, anti-inflammatory agents, antianxiety drugs, antitussive-expectorants, anti motion sickness agents, drugs for prevention and treatment for car-sickness, and so forth.

In case of the above (b), the orally disintegrable tablet is preferably used for preventing and/or treating hypertension, hyperlipemia, diabetes, bronchial asthma, cerebrovascular diseases, and so forth.

The "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention can be safely administered orally to mammals such as mice, rats, rabbits, cats, dogs, bovines, horses, monkeys, humans, etc.

With the dosage of the "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention, varies depending on the pharmaceutically active ingredient, subject, kinds of diseases, etc., the dosage can be selected so that the dosage of the pharmaceutically active ingredient is an effective amount.

For instance, when a benzimidazole compound (I) or a salt thereof such as lansoprazole is employed as an acid-labile physiologically active substance, especially a pharmaceutically active ingredient, the "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention is useful for treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, anastomotic ulcer, Zollinger-Ellison syndrome, etc), gastritis, reflux esophagitis, etc.; eradication of *H. pylori;* suppression of gastrointestinal bleeding caused by digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of gastrointestinal bleeding caused by invasive stress (e.g., stress caused by cerebrovascular disease, head injury, failure of many organs, burn injury of a wide range, which necessitate a large-scale operation necessitating the following intensive management, or intensive care); treatment and prevention of ulcer caused by non-steroidal anti-inflammatory agent; treatment and prevention of gastric hyperacidity and ulcer caused by postoperative stress; administration before anesthesia, etc. The dosage of the preparation per an adult (body weight: 60 kg) is about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, as a benzimidazole compound (I) or a salt thereof such as lansoprazole.

The "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention can be administered once a day, or two or three times separately a day.

BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples and Reference Examples are further illustrative but by no means limitative of the present invention.

Unless otherwise specifically indicated, the following "%" means weight %.

Also, the content of the hydroxypropoxyl group is measured in accordance with the methods described in Japanese Pharmacopoeia (13th edition).

The physical properties of the tablets and granules prepared in Examples were determined by the following test methods.

(1) Hardness Test

Determination was carried out with a tablet hardness tester [manufactured by Toyama Sangyo, Co. Ltd. (Japan)]. The test was performed in 10 runs and mean values were shown.

(2) Oral Disintegration Time

Time for complete disintegration only by saliva in the oral cavity was determined.

(3) Remaining Ratio

According to the 2nd method of the dissolution test defined in Japanese Pharmacopoeia, the dissolution test was performed by using 500 ml of 0.1N HCl (75 rpm) for 1 hour. Then, the enteric fine granule was collected by means of the sieve. The content of the drug in the collected fine granule was measured by the HPLC method. The remaining ratio was calculated according to the following expression with the content of the drug in the tablet which is measured separately by HPLC method.

Remaining ratio=(Content of the drug in the collected fine granule after the dissolution test using 0.1N HCl for 1 hour)/(Content of the drug in the tablet)

(4) Acid-resistance: Dissolution using 0.1N HCl

According to the 2nd method of the dissolution test defined in Japanese Pharmacopoeia, the dissolution test was performed by using 500 ml f 0.1N HCl (75 rpm) for hour. Then, test medium was collected and filtered by using a 0.45 μm membrane filter. The absorbance way measured to calculate the dissolution of the drug into 0.1N HCl.

(5) Average Particle Diameter: Volume Based Distribution Median Diameter (median diameter: 50% Particle Diameter from Cumulative Distribution)

Determination was carried out with Raser Diffraction Analyzer, type; HEROS RODOS [trade name, manufactured by Sympatec (Germany)].

EXAMPLES

Example 1

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] is charged with 300 g of Nonpareil 105 (70–140) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 28° C. respectively, the Nonpareil is coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation is stopped when the specified amount of the bulk liquid has been sprayed, and then drying is carried out in the granulator for 7 minutes. The resulting granules are sieved through a #60 circular sieve (250 Am) and a #100 circular sieve (150 μm) to provide 750 g of granules having a core.

Bulk Liquid:

Lansoprazole	300 g
Magnesium carbonate	100 g
L-HPC	50 g
HPC (Type SSL)	100 g
Water	1650 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] is charged with 680 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70°0 C. and about 36° C., respectively, an undercoating liquid of the following composition prepared in advance is sprayed in accordance with the tangential spray method at a spray rate of 10 g/min. to provide 650 g of film-undercoated granules having a core.

Undercoating Liquid:

HPMC (Type 2910, viscosity: 3 centistokes)	32 g
Talc	8 g
Water	760 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] is charged with 450 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 36° C., respectively, an enteric film coating liquid of the following composition prepared in advance is sprayed in accordance with the tangential spray method at a spray rate of 17 g/min. The coated powders are dried in vacuum at 40° C. for 16 hours, and sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 950 g of enteric coated granules having a core.

Enteric Film Coating Liquid:

Eudragit L30D-55	1078.3 g
Eudragit NE30D	138.5 g
Triethyl citrate	46.0 g
Glyceryl monostearate	23.1 g
Talc	16.0 g
Polysorbate 80	9.0 g
Yellow iron oxide	0.5 g
Water	2038.5 g

Sieve	weight ratio
#18 (850 μm) on	0%
#30 (500 μm) on	0%
#200 (75 μm) on	100%
#200 (75 μm) pass	0%

(4) Production of Granulated Powders

A fluidized bed granulator [manufactured by Powrex Corp. (Japan), LAB-1] is charged with 1321.2 g of erythritol [manufactured by Nikken Chemical Co., Ltd. (Japan)], 360.0 g of low-substituted hydroxypropyl cellulose LH-32 [hydroxypropoxyl group contents of 8.8 %, manufactured by Shin-Etsu Chemical Co., Ltd. (Japan)], 18.0 g of citric acid anhydrous, and 1.8 g of aspartame, and granulation is carried out while spraying a solution which is prepared by dissolving 3.6 g of polyethylene glycol (PEG-6000) in 896.4 ml of purified water. The granules are dried to provide granulated powders. To the granulated powders are added 90.0 g of crospovidone and 5.4 g of magnesium stearate, which is admixed in a bag to give mixed powders.

(5) Production of Orally Disintegrable Tablets

Hereinafter, the above "enteric coated granules having a core" is referred to as "enteric coated powders".

200.0 g of the above enteric coated powders and 300.0 g of the above mixed powders are tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 11 mm in diameter, at a tabletting pressure of 1.0 ton/cm^2 to provide tablets each weighing 500 mg.

Reference Example 1

An alkaline cellulose comprising 24.1% of NaOH, 1.7% of Na_2CO_3, 42.9% of cellulose, 31.8% of H_2O was obtained by immersing a wood pulp in 49% aqueous solution of sodium hydroxide and then by pressing it. A reactor was charged with 100 weight parts of the alkaline cellulose. Then, nitrogen gas replacement was carried out. After the replacement, 5 weight parts of propylene oxide was charged in the reactor and reacted with stirring at 40° C. for 1 hour, at 50° C. for 1 hour and at 70° C. for 1 hour to obtain 103 weight parts of a reactant.

On the other side, a kneader was charged with 2.5 weight parts of hot water at 65° C. and 0.13 weight parts of glacial acetic acid (about 40 weight % against equivalent for neutralization, initial neutralized acid) and therein, 1 weight part of the above resulting alkaline cellulose was dispersed. Then, the temperature was set at 30° C. to dissolve a part of the reactant, and 0.20 weight part of glacial acetic acid (the remainder of an equivalent for neutralization, complete neutralized acid) to obtain a processed fiber product containing a part of dissolution and a part of deposit.

The resulting product was washed with hot water at about 80° C., drained, dried, ground by means of a high rolling impact grinder, and sifted by means of a 100 mesh sieve to obtain the powder of low-substituted hydroxypropyl cellulose LH-33 (the content of hydroxypropoxyl group: 5.8 weight %, the average particle diameter: 17.8 μm).

Reference Example 2

Powders of low-substituted hydroxypropyl cellulose LH-23 (hydroxypropoxyl group contents: 5.7 weight %, average particle diameter: 30.8 μm) were obtained in the same manner as in Reference Example 1.

Example 2

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 300 g of Nonpareil 105 [(trade name) particle diameter: 100 to 200 μm]. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 30° C., respectively, the Nonpareil was coated by spraying a spray liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min., and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #48 circular sieve (300 μm) and a #100 circular sieve (150 μm) to provide 2186 g of powders (150 to 300 μm) having a core.

Spray Liquid:

Lansoprazole	927 g
Magnesium carbonate	309 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 wt %) (average particle diameter: 17.57 μm)	154.5 g
Hydroxypropyl cellulose (Type SSL)	309 g
Purified water	3955 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 2040 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 40° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 13 g/min. to provide 2145 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	264 g
Purified water	5016 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1710 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 40° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 17 g/min., and dried for 7 minutes, and then sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 2393 g of enteric coated powders (177 to 355 μm) having a core.

Enteric Film Coating Liquid:

Eudragit L30D-55	5016.4 g
Eudragit NE30D	559.0 g
Triethyl citrate	333.7 g
Glyceryl monostearate	106.5 g
Polysorbate 80	34.8 g
Red iron oxide	1.8 g
Purified water	2547.1 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 600 g of the above enteric coated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 32° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 11 g/min., and then dried for 7 minutes to provide 617 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 334.1 μm.

Film Coating Liquid:

Mannitol	33 g
Purified water	297 g

(5) Production of Mannitol-granulated Powders

A fluidized bed granulator [manufactured by Powrex Corp. (Japan), LAB-1] was charged with 800 g of mannitol [manufactured by Merck Japan Co., Ltd.], and granulation was carried out while spraying 315 g of purified water. The granules were dried to provide 727.3 g of granulated powders.

(6) Production of Mixed Powders

To 97.3 g of the above mannitol-granulated powders were added 105 g of the above enteric coated and mannitol coated granules having a core, 15.0 g of low-substituted hydrox-

ypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %, average particle diameter: 17.8 μm), 22.5 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 7.5 g of crospovidone, 1.5 g of citric acid anhydrous, 0.45 g of aspartame and 0.75 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(7) Production of Orally Disintegrable Tablets

250.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch (15R), 11 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 5.9 kg and 30 seconds, respectively.

Example 3

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 900 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 29° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 5654.7 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #60 circular sieve (250 μm) and a #100 circular sieve (150 μm) to provide 2424 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4608 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)) was charged with 2337.5 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 41° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 18 g/min. The spraying operation was stopped when the specified amount 6050 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes to provide 2551 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropyl methylcellulose (Type 2910, viscosity: 3 centistokes)	332.5 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %) (average particle diameter: 17.57 μm)	17.5 g
Purified water	6650 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 570 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 40° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 18 g/min. The spraying operation was stopped when the specified amount 2646 g of the enteric film coating liquid had been sprayed, and then drying was carried out in the granulator for 8 minutes. The coated powders were sieved through a #42 circular sieve (355 μm) and a #70 circular sieve (212 μm) to provide 1116 g of enteric coated granules having a core.

The average particle diameter of the obtained granules was 326.9 μm.

Enteric Film Coating Liquid:

Eudragit L30D-55	1911 g
Eudragit NE30D	212.9 g
Triethyl citrate	127.1 g
Glyceryl monostearate	40.6 g
Polysorbate 80	13.3 g
Red iron oxide	0.8 g
Purified water	970.3 g

(4) Production of Mixed Powders

To 200 g of the above enteric coated granules having a core were added 189.7 g of mannitol, 30.0 g of low-substituted hydroxypropyl cellulose LH-23 (hydroxypropoxyl group contents: 5.8 weight %, average particle diameter: 17.8 μm), 60.0 g of crystalline cellulose RCEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15.0 g of crospovidone, 2.8 g of citric acid anhydrous and 25 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(5) Production of Orally Disintegrable Tablets

250.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch (15R), 11 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 4.2 kg and 24 seconds, respectively.

Example 4

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (TyDp 2)] was charged with 900 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 32° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation was stopped when the specified amount 5654.7 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #48 circular sieve (300 μm) and a #100 circular sieve (150 μm) to provide 2280 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4608 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1020 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 40° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 15 g/min. The spraying operation was stopped when the specified amount 1980 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes to provide 1330.5 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	120 g
Titanium oxide (TiO_2)	240 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	240 g
Magnesium carbonate	120 g
Purified water	2880 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan)], MP-10 (Type 2)1 was charged with 460 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 41° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 13 g/min. The spraying operation was stopped when the specified amount 2205 of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid:

Eudragit L30D-55	2290 g
Eudragit NE30D	253 g
Triethyl citrate	153 g
Glyceryl monostearate	20 g
Polysorbate 80	8 g
Titanium oxide (TiO_2)	53 g
Sterilized Talc H (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	53 g
Purified water	2420 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 35° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 16 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex dorD. (Japan), MP-10 (Type 2)].

The spraying operation was stopped when the specified amount 824 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minute. The resulting granules were sieved through a #42 circular sieve (355 μm) and a #60 circular sieve (250 μm) to provide 806 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 326.6 μm.

Film Coating Liquid:

Mannitol	320 g
Purified water	2880 g

(5) Production of Mixed Powders

To 120 g of the above enteric coated and mannitol coated granules having a core were added 87.75 g of mannitol, 8.5 g of low-substituted hydroxypropyl cellulose LH-23 (hydroxypropoxyl group contents: 5.8 weight %), 4.5 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 19.5 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 6.5 g of crospovidone, 1.3 g of citric acid anhydrous, 1.3 g of aspartame and 0.65 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

250.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch (15R), 11 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.9 kg and 20.5 seconds, respectively.

The remaining ratio of the obtained tablet after acid-resistance test was 97%.

Example 5

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 900 g of Nonpareil 1.05 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 30° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the Specified amount 5661 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 8 minutes The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2074 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4680 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged

with 2074 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 78° C. and about 40° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 1980 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 9 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2555 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	252 g
Titanium oxide (TiO_2)	108 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	108 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Mannitol	252 g
Purified water	3600 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1320 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 42° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance With the tangential spray method at a spray rate of 22 g/min. The specified amount 1638 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	1219.2 g
Eudragit NE30D	134.4 g
Polyethylene glycol 6000	40.8 g
Glyceryl monostearate	24.0 g
Polysorbate 80	7.2 g
Ferric oxide	0.24 g
Ferric oxide (yellow)	0.24 g
Citric acid anhydrous	0.48 g
Purified water	1693 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 76° C. and about 42° C., respectively, an enteric film coating liquid (B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 6552 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	4032 g
Eudragit NE30D	447.8 g
Triethyl citrate	269.3 g
Glyceryl monostearate	86.4 g
Polysorbate 80	25.9 g
Ferric oxide	0.86 g
Ferric oxide (yellow)	0.86 g

-continued

Citric acid anhydrous	0.72 g
Purified water	2624 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 42° C., respectively, an enteric film coating liquid (A) of the above mentioned composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 819 g of the enteric film coating liquid had been sprayed.

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), with the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 35° C., respectively an f film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 882 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 1964 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 333.7 μm.

Film coating liquid:

Mannitol	180 g
Purified water	1080 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 204.0 g of mannitol, 30 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of crospovidone, 3 g of citric acid anhydrous, 9 g of aspartame, 6 g of magnesium stearate and 3 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 13 mm in diameter, at a tabletting pressure of 1.5 ton/Cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 2.6 kg and 20 seconds, respectively.

The acid-resistance of the obtained tablet was 3.5%.

Example 6

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 750 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 30° C. respectively, the Nonpareil was coated by

spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 4717. 5 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 8 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 1811 g of granules having a core.

Bulk Liquid:

Lansoprazole	900 g
Magnesium carbonate	300 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	150 g
Hydroxypropyl cellulose (Type SSL)	300 g
Purified water	3900 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1811 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 78° C. and about 38° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray imethod at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 5274 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 9 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2628 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	378 g
Titanium oxide (TiO_2)	162 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	162 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	270 g
Mannitol	378 g
Purified water	5400 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1560 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 40° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The specified amount 6048 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	4032 g
Eudragit NE30D	447.8 g
Triethyl citrate	269.3 g
Glyceryl monostearate	86.4 g
Polysorbate 80	25.9 g
Ferric oxide	0.86 g
Ferric oxide (yellow)	0.86 g
Citric acid anhydrous	0.72 g
Purified water	2624 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 72° C. and about 42° C, respectively, an enteric film coating liquid (B) of the following composition preepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The specified amount 819 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	609.6 g
Eudragit NE30D	68.0 g
Polyethylene glycol 6000	20.4 g
Glyceryl monostearate	12.0 g
Polysorbate 80	3.6 g
Ferric oxide	0.12 g
Ferric oxide (yellow)	0.12 g
Citric acid anhydrous	0.24 g
Purified water	846.7 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), while the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 38° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 882 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 17 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 2825 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 330.5 μm.

Film Coating Liquid:

Mannitol	180 g
Purified water	1080 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 204.0 g of mannitol, 30 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KC-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of crospovidone, 3 g of citric acid anhydrous, 9 g of aspartame, 6 g of magnesium stearate and 2 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 13 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.1 kg and 22 seconds, respectively.

The acid-resistance of the obtained tablet was 2.5%.

Example 7

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 750 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 30° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation was stopped when the specified amount 4717.5 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes to provide 1842 g of granules having a core.

Bulk Liquid:

Lansoprazole	900 g
Magnesium carbonate	300 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	150 g
Hydroxypropyl cellulose (Type SSL)	300 g
Purified water	3900 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fliudized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1842 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 74° C. and about 38° C., respectively, an undercoating liquid of the following composition prepared an advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The spraying operation was stopped when the specified amount 5365 g of the undercoatingliquid had been sprayed, and then drying was carried out in the granulator for 9 minutes. The resulting granules were sieved through a#42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2770 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	378 g
Titanium oxide (TiO_2)	162 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	162 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	270 g
Mannitol	378 g
Purified water	5400 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1300 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 78° C. and about 39° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 21 g/min. The spraying operation was stopped when the specified amount 5040 g of the enteric film coating liquid had been sprayed, and then drying was carried out in the granulator for 16 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 2453 g of enteric coated granules having a core.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	4032 g
Eudragit NE30D	447.8 g
Triethyl citrate	269.3 g
Glyceryl monostearate	86.4 g
Polysorbate 80	25.9 g
Ferric oxide	0.86 g
Ferric oxide (yellow)	0.86 g
Citric acid anhydrous	0.72 g
Purified water	2624 g

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1000 g of the above enteric coated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 38° C., respectively, an enteric film coating liquid (B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The specified amount 273 g of the enteric film coating liquid had, been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	610.4 g
Eudragit NE30D	68.0 g
Polyethylene glycol 6000	20.4 g
Glyceryl monostearate	12.0 g
Polysorbate 80	3.6 g
Ferric oxide	0.12 g
Ferric oxide (yellow)	0.12 g
Citric acid anhydrous	0.24 g
Purified water	845.12 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), while the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 35° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 20 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 294 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 1061 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 307.1 μm.

Film Coating Liquid:

Mannitol	120 g
Purified water	720 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 207 g of mannitol, 30 g

of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of crospovidone, 3 g of citric acid anhydrous, 9 g of aspartame, 6 g of magnesium stearate and 3 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 13 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.2 kg and 24 seconds, respectively.

Example 8

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 900 g of Nonpareil 105T (trade name) (particle diameter of 100 to 200 m). With the inlet air temperature and the temperature of the loading being controlled at 71 to 78° C. and about 31° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 21 g/min. The spraying operation was stopped when the specified amount 5550 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 21 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 1723 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4680 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluided coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 2074 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 77° C. and about 41° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 21 g/min. The spraying operation was stopped when the specified amount 2787 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 13 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 1958 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	252 g
Titanium oxide (TiO_2)	108 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	108 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Mannitol	252 g
Purified water	3600 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized Goating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1100 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 41° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 1365 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	1017.3 g
Eudragit NE30D	113.3 g
Polyethylene glycol 6000	34.0 g
Glyceryl monostearate	20.0 g
Polysorbate 80	6.0 g
Ferric oxide	0.2 g
Ferric oxide (yellow)	0.2 g
Citric acid anhydrous	0.4 g
Purified water	1410.8 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 76° C. and about 41° C., respectively, an enteric film coating liquid (B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 5040 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	3360 g
Eudragit NE30D	373.2 g
Triethyl citrate	224.4 g
Glyceryl monostearate	72.0 g
Polysorbate 80	21.6 g
Ferric oxide	0.72 g
Ferric oxide (yellow)	0.72 g
Citric acid anhydrous	0.6 g
Purified water	1706.8 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 42° C., respectively, an enteric film coating liquid (A) of the above mentioned composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 21 g/min. The specified amount 682.5 g of the enteric film coating liquid had been sprayed.

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 36° C., respectively, an film coating liquid of the

following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 735 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 2319.5 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules; was 392.7 μm.

Film Coating Liquid:

Mannitol	100 g
Purified water	600 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 204.0 g of mannitol, 30 g of low-substituted hyaroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of [crospovidone, 3 g of citric acid anhyaroug, 9 g of dspartame, 6 g of magnesium stearate and 3 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 12 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.7 kg and 35 seconds, respectively.

The acid-resistance of the obtained tablet was 3.4%.

Example 9

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator (manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 300 g of Nonpareil 105 (70–140) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 28° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation was stopped when the specified amount of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 7 minutes. The resulting granules were sieved through a #48 circular sieve (300 μm) and a #100 circular sieve (150 μm) to provide 757 g of granules having a core.

Bulk Liquid:

Lansoprazole	300 g
Magnesium carbonate	100 g
L-HPC	50 g
HPC (Type SSL)	100 g
Water	1650 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 680 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 36° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 10 g/min. to provide 672 g of film-undercoated granules having a core.

Undercoating Liquid:

HPMC (Type 2910, viscosity: 3 centistokes)	32 g
Talc	8 g
Water	760 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 450 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 36° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a sprayer rate of 17 g/min. The Coated powders were dried in vacuum at 40° C. for 16 hours, and sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 950 g of enteric coated granules having a core.

The average particle diameter of the obtained granules was 285.4 μm.

Enteric Film Coating Liquid:

Eudragit L30D-55	1078.3 g
Eudragit NE30D	138.5 g
Triethyl citrate	46.0 g
Glyceryl monostearate	16.5 g
Talc	16.0 g
Polysorbate 80	9.0 g
Iron oxide	0.5 g
Water	2038.5 g

Sieve	weight ratio
#18 (850 μm) on	0%
#30 (500 μm) on	0%
#200 (75 μm) on	100%
#200 (75 μm) pass	0%

(4) Production of Granulated Powders

A fluidized bed granulator [manufactured by Powrex Corp., (Japan), LAB-1] was charged with 1321.2 g of erythritol [manufactured by Nikken Chemical Co., Ltd. (Japan)], 360.0 g of low-substituted hydroxypropyl cellulose LH-32 [hydroxypropoxyl group contents of 8.8%, manufactured by Shin-PteU Chemical Co., Ltd. (Japan)], 18.0 g of citric acid anhydrous, and 1.8 g of aspartame, and granulation was carried out while spraying a solution which was prepared by dissolving 3.6 g of polyethylene glycol (PEG-6000) in 896.4 ml of purified water. The granules were dried

to provide granulated powders. To the granulated powders were added 90.0 g of crospovidone and 5.4 a of magnesium stearate, which was admixed in a bag to give mixed powders.

(5) Production of Orally Disintegrable Tablets

200.0 g of the above enteric coated granules having a core and 300.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 11 mm in diameter, at a tabletting pressure of 1.0 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness, the oral disintegration time and remaining ratio after acid-resistance test of each tablet thus obtained were 4.2 kg, 27 seconds and 96.3%, respectively.

INDUSTRIAL APPLICABILITY

The orally disintegrable tablet of the present invention has superior disintegrability or dissolution so that it can be used for treatment or prevention of various diseases, as an orally disintegrable tablet capable of being administered to the aged of children and easily administered without water. Also, because the orally disintegrable tablet of the present invention contains fine granules having the average particle diameter and an enteric coating layer such that it will not impart roughness in mouth, it can be administered easily without discomfort at the administration and has superior acid-resistance.

Further, because the orally disintegrable tablet of the present invention has a suitable strength such that it will not be substantially damaged through production processes or circulation processes, it is superior in stability for long-term storage and easy of use at the administration.

Further, because the fine granule of the present invention is characterized in that it stably retains the acid-labile physiologically active substance, contains the physiologically active substance in high content, be small and has superior stability, it can be used for producing various compact pharmaceutical preparations such as tablets, capsules, suspensions and so forth. Such preparations are easy of use at the administration. In addition, the fine granule of the present invention has superior acid-resistance after compression.

What is claimed is:

1. An orally disintegrable tablet which comprises

(i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent, said composition having 10 weight % or more of an acid-labile physiologically active substrate that is lansoprazole and (ii) an additive wherein said tablet having a hardness strength of about 1 to about 20 kg, is orally disintegrable.

2. An orally disintegrable tablet of claim **1**, wherein the average particle diameter of the fine granule is 300 to 400 μm.

3. An orally disintegrable tablet of claim **1**, wherein the fine granules further comprise a basic inorganic salt.

4. An orally disintegrable tablet of claim **1**, wherein the additive comprises a water-soluble sugar alcohol.

5. An orally disintegrable tablet of claim **1**, wherein the composition coated by an enteric coating layer is further coated by a coating layer which comprises a water-soluble sugar alcohol.

6. An orally disintegrable tablet of claim **4**, wherein the additive comprises (1) crystalline cellulose and/or (ii) low-substituted hydroxypropyl cellulose.

7. An orally disintegrable tablet of claim **1**, wherein the particle diameter of the fine granules is practically 425 μm or less.

8. An orally disintegrable tablet of claim **1**, wherein the particle diameter of the fine granules is practically 400 μm or less.

9. An orally disintegrable tablet of claim **3**, wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium.

10. An orally disintegrable tablet of claim **1**, wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose.

11. An orally disintegrable tablet of claim **10**, wherein the core comprises 50 weight % or more of lactose.

12. An orally disintegrable tablet of claim **10**, wherein the core comprises 40 to 50 weight % of crystalline cellulose and 50 to 60 weight % of lactose.

13. An orally disintegrable tablet of claim **1**, wherein the composition comprises 20 weight % or more of an acid-labile physiologically active substance.

14. An orally disintegrable tablet of claim **1**, wherein the composition comprises 20 to 50 weight % of an acid-labile physiologically active substance.

15. An orally disintegrable tablet of claim **1**, wherein the fine granules are produced by fluidized-bed granulation method.

16. An orally disintegrable tablet of claim **1**, wherein the enteric coating layer comprises an aqueous enteric polymer agent.

17. An orally disintegrable tablet of claim **16**, wherein the aqueous enteric polymer agent is a methacrylate copolymer.

18. An orally disintegrable tablet of claim **1**, wherein the sustained-release agent is a methacrylate copolymer.

19. An orally disintegrable tablet of claim **16**, wherein the sustained-release agent is in an amount of 5 15 weight % relative to 100 weight % of the aqueous enteric polymer agent.

20. An orally disintegrable tablet of claim **4**, wherein the water-soluble sugar alcohol is erythritol.

21. An orally disintegrable tablet of claim **4**, wherein the water-soluble sugar alcohol si mannitol.

22. An orally disintegrable tablet of claim **5**, wherein the water-soluble sugar alcohol is in an amount of 5 to 97 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

23. An orally disintegrable tablet of claim **4**, wherein the crystalline cellulose is in an amount of 3 to 50 weight % relative to 100 weight % of the tablet apart from the fine granule.

24. An orally disentegrable tablet of claim **6**, wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropyl cellulose is 7.0 to 9.9 weight %.

25. An orally disintegrable tablet of claim **6**, wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropoxyl cellulose is 5.0 7.0 weight %.

26. An orally disintegrable tablet of claim **1**, which further comprises crosprovidone.

27. An orally disintegrable tablet of claim **1**, wherein the oral disintegration time is one minute or less.

28. An orally disintegrable tablet of claim **1**, which comprises no lubricant inside the tablet.

29. Fine granules having an average particle diameter of 400 μm or less, which comprise a composition coated by an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent, said composition having (i) 25

weight % or more of an acid-liable physiologically active substance that is lansoprazole and (ii) a basic inorganic salt.

30. Fine granules of claim **28**, wherein the average particle diameter of the fine granules is 300 to 400 μm.

31. Fine granules of claim **28**, wherein the particle diameter of the fine granules is practically 425 μm or less.

32. Fine granules of claim **28**, wherein the particle diameter of the fine granules is practically 400 μm or less.

33. Fine granules of claim **28**, wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium.

34. Fine granules of claim **28**, wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose.

35. Fine granules of claim **34**, wherein the core comprises 50 weight % or more of lactose.

36. Fine granules of claim **28**, wherein the composition comprises 25 to 40 weight % of an acid-labile physiologically active substance.

37. Fine granules of claim **28**, which are produced by fluidized-bed granulation method.

38. Fine granules of claim **28**, wherein the enteric coating layer comprises an aqueous enteric polymer agent.

39. Fine granules of claim **38**, wherein the aqueous enteric polymer agent is a methacrylate copolymer.

40. Fine granules of claim **28**, wherien the sustained-release agent is a methacrylate copolymer.

41. Fine granules of claim **28**, wherein the sustained-release agent is in an amount of 5 to 15 weight % relative to 100 weight % of the aqueous enteric polymer agent.

42. Fine granules of claim **28**, wherein the enteric coating layer is in an amount of 50 to 70 weight % relative to 100 weight % of the fine granules.

43. A tablet, granule, fine granule, capsule, effervescent or suspension preparation which comprises the fine granules of claim **28**.

44. An orally disintegrable tablet of claim **16**, wherein the sustained-release agent is in an amount of 5 to 30 weight % relative to 100 weight % of the aqueous enteric polymer agent.

45. Fine granules of claim **38**, wherein the sustained-release agent is in an amount of 5 to 30% relative to 100 weight % of the aqueous enteric polymer agent.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,328,994 B1
DATED : December 11, 2001
INVENTOR(S) : Toshihiro Shimizu, Shuji Morimoto and Tetsuo Tabata

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 37,
Line 8, the word "substrate" should read -- substance --

Column 38,
Line 2, the word "si" should read -- is --

Signed and Sealed this

Fifth Day of August, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office